EXPLORING THE DIAGNOSIS OF CLUSTER HEADACHE:

A MULTI-METHOD STUDY

Alina Buture MD

PhD in Medical Sciences

The University of Hull and the University of York

Hull York Medical School

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'Science never solves a problem without creating ten more'.

George Bernard Shaw

Abstract

Background: Cluster headache (CH) is a severe primary headache affecting 1/1000 people of the general population. The diagnostic delay, misdiagnosis and mismanagement of CH are well evidenced in the literature. The aim of this doctoral research is to understand the under-recognition by exploring the diagnosis of CH.

Methods: Multi-method study comprised of four main parts:

(1) A systematic literature review on the delays in diagnosis and misdiagnosis of CH;

(2) A literature review on the pathophysiology of CH;

(3) A prospective observational study of a novel screening tool with images depicting headache pain that could differentiate between CH and migraine. Images depicting headache pain were assessed on healthy participants to test if they depict a range of pain severities. The screening tool was tested and refined in a pilot study and subsequently assessed in a larger-scale study. The total screening tool score (which ranged between 3-32) was used as predictor of CH.

(4) A qualitative study with semi-structured interviews that explored the perceptions on the CH diagnosis among three key stakeholder groups: participants with CH, GPs and neurologists.

Results:

(1) The systematic literature review brought together the existing evidence on diagnostic delays, numerous misdiagnosis, consultation of multiple clinicians and mismanagement of CH.

(2) The literature review on the pathophysiology of CH summarised the research on the biomedical aspects of CH and informed on the imaging, peptide and genetic studies in CH.

(3) Six images depicting headache pain tested on 150 healthy participants showed a range of severities from mild to excruciating. The screening tool was piloted on 100 patients with migraine and 16 patients with CH. The refined screening tool was assessed on 81 patients with CH and 215 patients with migraine. Patients with CH had a higher mean test score compared to patients with migraine (28.4 versus 19.5). At a cut-off score of >25 out of 32, the screening tool for CH had a sensitivity of 86.4% and a specificity of 92.0%.

(4) The qualitative data set that included 26 patients with CH, eight GPs and eight neurologists identified prolonged diagnostic journey of CH with significant impact on social life and mental health. Both patient and clinician's factors are involved in the diagnostic delay.

Conclusions: This multi-method study identified challenges around the timely diagnosis of CH and multiple factors involved in the under-recognition of CH. The screening tool could be a useful instrument to aid the diagnosis of CH. Validation in other medical settings including primary care is required.

Table of contents

CHAPTER 1. CONCEPTUALIZING THE DIAGNOSIS OF CLUSTER HEADACHE 1

1.1 Introducing cluster headache 1

1.1.1 Clinical manifestations 1

1.1.2 Management 5

1.2 Study objectives and research questions 5

CHAPTER 2. SYSTEMATIC LITERATURE REVIEW ON THE DELAYS IN DIAGNOSIS AND MISDIAGNOSIS OF CLUSTER HEADACHE 11

2.1 Introduction 11

2.2 Aim and objectives 11

2.3 Methods 11

2.3.1 Search strategy 11

2.3.2 Data extraction, assessment and analysis 13

2.3.3 Quality assessment of the included studies 13

2.4 Results 14

2.4.1 Study characteristics 14

2.4.2 Participants' characteristics 16

2.4.3 Non-English articles 16

2.4.4 Quality assessment of the included studies 23

2.4.5 Diagnostic delays 26

2.4.6 Misdiagnoses 27

2.4.7 Mismanagement 27

2.4.8 Clinicians seen prior to correct diagnosis 27

2.4.9 Factors involved in diagnostic delay 28

2.5 Discussion 29

2.5.1 Delays in diagnosis 29

2.5.2 Misdiagnosis and mismanagement 30

2.5.3 Factors involved in diagnostic delays 31
2.5.4 Strengths and limitations 32
2.5.5 Summary of articles published between 2017 and 2020 32

2.6 Conclusions 33

CHAPTER 3. PATHOPHYSIOLOGY OF CLUSTER HEADACHE: A LITERATURE REVIEW 34

3.1 Introduction 34

3.2 Methods 34

3.3 Results 35
3.3.1 Neuroimaging studies 35
3.3.1.1 Structural studies 35
3.3.1.2 Functional studies 37
3.3.1.3 Biochemical studies 39
3.3.2 The trigeminovascular pain pathways and neuropeptides 44
3.3.2.1 Anatomy of the trigeminovascular pain pathways 44
3.3.2.2 Activation of the trigeminovascular system 45
3.3.2.3 Neuropeptide studies 47
3.3.3 Genetic aspects of CH 51
3.3.3.1 Hypocretin neuropeptide precursor gene 51
3.3.3.2 Alcohol dehydrogenase 4 gene 52
3.3.3.3 Circadian locomotor output cycles kaput gene 52
3.3.3.4 CACNA1A gene 52

3.4 Discussion 53
3.4.1 The role of neuroimaging studies in CH 53
3.4.2 The role of neuropeptides and genetic studies in CH 55
3.4.3 Strengths and limitations 55

3.5 Conclusions 56

CHAPTER 4. DEVELOPMENT AND EVALUATION OF A SCREENING TOOL FOR THE DETECTION OF CLUSTER HEADACHE – A PROSPECTIVE OBSERVATIONAL STUDY **57**

4.1 Introduction **57**

4.2 Background to CH diagnosis **57**

4.2.1 Challenges with the detection of CH 57

4.2.2 Key differences between CH and migraine 58

4.2.2.1 Clinical characteristics 59

4.2.2.2 Management 61

4.2.3 Assessing existing screening tools for CH 62

4.2.4 Existing visual tools for pain assessment 66

4.3 Study objectives **68**

4.4 Primary and secondary outcomes **68**

4.5 Methodology **69**

4.5.1 Study design 69

4.5.1.1 Phase I: Screening tool development 70

4.5.1.2 Phase II: Pilot study 74

4.5.1.3 Phase III: Larger-scale study 74

4.5.2 Statistical methodology 74

4.5.2.1 Descriptive analysis of the test scores 74

4.5.2.2 Correspondence analysis of the test scores 77

4.5.2.3 Sensitivity, specificity statistics and the ROC analysis 78

4.6 Results **80**

4.6.1 Phase I: Screening tool development 80

4.6.1.1 Assessment of images on healthy participants 80

4.6.1.2 Verbal descriptions of pain 84

4.6.1.3 Key questions that could differentiate between CH and migraine 85

4.6.2 Phase II: Pilot study 88

4.6.2.1 Demographic profile of the study population 88

4.6.2.2 Patients' feedback on the screening tool 88

4.6.2.3 Descriptive analysis of the findings 91
4.6.3 Phase III: Larger-scale study 93
4.6.3.1 Description of the sample 93
4.6.3.2 Descriptive analysis of test scores 95
4.6.3.3 Correspondence analysis of the test scores 99
4.6.3.4 Sensitivity and specificity statistics for items with dichotomous responses 102
4.6.3.5 Determining the overall performance of the screening tool 106

4.7 Discussion 109
4.7.1 Profile of patients with headache 110
4.7.2 Clinical indicators of CH versus migraine 110
4.7.3 The screening tool's role in detecting CH 112
4.7.4 Strengths and limitations 114

4.8 Conclusions 115

CHAPTER 5. EXPERIENCES, UNDERSTANDINGS AND PERCEPTIONS ON CLUSTER HEADACHE DIAGNOSIS: A QUALITATIVE STUDY 117

5.1 Introduction 117

5.2 Qualitative and sociological research on primary headaches 117

5.3 Relevant theoretical concepts from medical sociology 118
5.3.1 Sociology of diagnosis 119
5.3.2 The doctor- patient relationship 120
5.3.3 Chronic illness and the notion of 'biographical disruption' 121
5.3.4 Biopsychosocial model of illness 122

5.4 CHIPS study 123

5.5 Methods 123
5.5.1 Study design 123
5.5.2 Setting and data collection 123
5.5.3 Data analysis 125

5.6 Results 126

5.6.1 Research participants' profile in the CHIPS study 126
5.6.2 Twenty-six diagnostic journeys of CH 129
5.6.3 Four main themes on the diagnosis of CH 132
5.6.3.1 Lay diagnosis 134
5.6.3.2 Delays in diagnosis 135
5.6.3.3 Misdiagnosis and mismanagement 137
5.6.3.4 Establishing the diagnosis of CH 139

5.7 Discussion 141
5.7.1 Perceptions of CH diagnosis among clinicians 141
5.7.2 The impact of CH 142
5.7.3 Factors contributing to delayed diagnosis of CH 145
5.7.4 Stenghts and limitations 148

5.8 Conclusions 148

CHAPTER 6. GENERAL DISCUSSION AND CONCLUSIONS 150

6.1 Introduction 150

6.2 Integration of findings 150
6.2.1 Point of seeking healthcare 153
6.2.2 Delays in diagnosis 155
6.2.2.1 Types of misdiagnosis 155
6.2.2.2 Factors involved in delays 156
6.2.2.3 Impact of challenges in diagnostic journey 160
6.2.3 Obtaining correct diagnosis 161
6.2.3.1 Clinicians' and patients' perception on diagnosis 161
6.2.3.2 Assessing the value of screening tools for CH 162

6.3 Implications for clinical practice 165

6.4 Personal reflection 167

6.5 Future work 168

6.6 Conclusions 169

REFERENCES **170**

APPENDICES **200**

Appendix 1. Databases and search criteria to identify articles on delays in diagnosis and misdiagnosis of CH 200

Appendix 2. The Joanna Briggs Institute (JBI) Critical Appraisal tool for case series 203

Appendix 3. Oxford Centre for Evidence Based Medicine (OCEBM) Critical Appraisal of Survey Studies 204

Appendix 4. Screening tool tested on patients with migraine 205

LIST OF ABBREVIATIONS **207**

List of tables

Table 1.1. The ICHD-3 criteria of primary headaches 2
Table 1.2. The diagnostic criteria of CH (ICHD-3) 4
Table 1.3. Study flow and thesis dissemination 7
Table 2.1. Inclusion and exclusion criteria 12
Table 2.2. Data extracted from case series and survey studies 17
Table 2.3. Factors involved in diagnostic delays 21
Table 2.4. Critical appraisal of case series using the JBI appraisal tool 24
Table 2.5. Critical appraisal of survey studies using the OCEBM appraisal tool 25
Table 3.1. Neuroimaging studies 40
Table 3.2. Craniovascular nerve fibres and their vasoactive neuropeptides 46
Table 4.1 Clinical features of CH versus migraine 60
Table 4.2. Management of CH versus migraine 62
Table 4.3. Existing screening tools for the detection of CH 64
Table 4.4. Variables measured with the 12-item screening tool 76
Table 4.5. Computation of total score 77
Table 4.6. Test items with dichotomous responses 79
Table 4.7. Test items with ordinal responses 79
Table 4.8. Image rating according to severity 81
Table 4.9. Questions provided by the headache experts that could differentiate between CH and migraine 85
Table 4.10. Demographic profile of the study population 88
Table 4.11 Screening tool amendments based on patients' feedback 89
Table 4.12. Headache characteristics classified by diagnosis 92
Table 4.13 Gender distribution of patients with CH and migraine 94
Table 4.14. Frequency distribution of ordinal test scores 96
Table 4.15. Frequency distribution of nominal test scores 97
Table 4.16. Association between test items according to the correspondence maps 101
Table 4.17. Sensitivity and specificity statistics for ‘description of pain’ 103
Table 4.18. Sensitivity and specificity statistics for ‘restlessness’ 103
Table 4.19. Sensitivity and specificity statistics for ‘excruciating agony’ 103
Table 4.20. Sensitivity and specificity statistics for ‘headache at specific time’ 103

Table 4.21. Sensitivity and specificity statistics for ‘strictly unilateral pain’ 104
Table 4.22. Sensitivity and specificity statistics for ‘ipsilateral cranial autonomic symptoms’ 104
Table 4.23. Sensitivity and specificity statistics for ‘untreated attack duration’ 104
Table 4.24. Sensitivity and specificity statistics for ‘treated attack duration’ 104
Table 4.25. Summary of sensitivity and specificity statistics for the eight items with binary responses 105
Table 4.26. Cut-off points on the ROC curves for whole data set 107
Table 4.27. ROC cut-off points for the male and female groups 108
Table 5.1. Extract from topic guide for participants with CH with illustrative questions 124
Table 5.2. Extract from topic guide for GPs and neurologists with illustrative questions 125
Table 5.3. Neurologists’ profile in the CHIPS study 127
Table 5.4. GPs’ profile in the CHIPS study 127
Table 5.5. CH participants’ profile in the CHIPS study 128
Table 6.1. Integration of findings: common themes among several chapters 151
Table 6.2. Point of seeking healthcare 154
Table 6.3. Types of CH misdiagnosis 156
Table 6.4. Factors involved in diagnostic delays 159
Table 6.5. Clinical indicators of CH 164

List of figures

Figure 1.1. Cranial autonomic features during a CH attack 3

Figure 1.2. The restlessness associated with the CH attacks 3

Figure 2.1. PRISMA Flow diagram 15

Figure 3.1. The ascending pathways of the trigeminovascular system 45

Figure 4.1. Photographic images (pain cards) used during pain consultations 66

Figure 4.2. Drawings of children with headache depicting pounding pain 67

Figure 4.3. Study flow 69

Figure 4.4. Images depicting headache pain illustrating different severities 71

Figure 4.5. Questionnaire with images depicting headache pain assessed on healthy participants 73

Figure 4.6. Images depicting headache pain and the answer distribution 83

Figure 4.7. Verbal descriptions of headache attacks 85

Figure 4.8. Key questions included in the screening tool 86

Figure 4.9. Screening tool for CH 87

Figure 4.10. Refined screening tool for CH 90

Figure 4.11. Mean age ± 95% CI of patients classified by diagnosis 94

Figure 4.12. Frequency distribution of total score 98

Figure 4.13 Mean total score ± 95% CI of patients classified by diagnosis 99

Figure 4.14. Correspondence maps between the image preference and other test items 100

Figure 4.15. ROC curves for whole data set 107

Figure 4.16. ROC curves according to gender 108

Figure 4.17. ROC curve of the total score after class balancing 109

Figure 4.18. Images depicting different pain severities 113

Figure 5.1. Summary of the four main themes on the diagnosis of CH 133

Figure 5.2. Factors involved in the prolonged diagnostic journey of CH 146

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Author's declaration

I confirm that this work is original and that if any passages or diagrams have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the references is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources. I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised.

CHAPTER 1. CONCEPTUALIZING THE DIAGNOSIS OF CLUSTER HEADACHE

The study of the brain is intimidating for many medical students, but has also been the source of fascination for many scientists, philosophers and artists. My captivation with the intricacies of the human brain started in medical school and was the impetus for choosing neurology as a medical speciality.

I started my training in Neurology in Bucharest (Romania) and continued specialist training through a Fellowship in Headache studies in the Neurology Department at Hull University Teaching Hospitals NHS Trust, UK. As a chronic migraineur myself, I have delved with curiosity into the complexities of the headache field. My fascination with cluster headache (CH) started when I joined the Cluster Headache-Impact and Perception Study (CHIPS) research team in 2015. In addition to that, dealing with misdiagnosed and mismanaged cases of CH determined me to pursue this as topic for my doctoral research.

1.1 Introducing cluster headache

In this section, I first outline the clinical manifestations of CH and I continue with a section on the management of CH.

1.1.1 Clinical manifestations

The International Classification of Headache Disorders (ICHD-3) classifies headache disorders into primary headaches and secondary headaches (1). According to the ICHD-3, primary headaches are classified into migraine, tension-type headache (TTH), trigeminal autonomic cephalalgias (TACs) and other primary headaches (1). The four main categories of primary headaches are shown in Table 1.1.

Table 1.1. The ICHD-3 criteria of primary headaches

1.	Migraine
2.	Tension-type headache (TTH)
3.	Trigeminal autonomic cephalalgias (TACs)
	3.1 Cluster headache 3.1.1. Episodic cluster headache 3.1.2. Chronic cluster headache 3.2. Paroxysmal hemicrania 3.2.1 Episodic paroxysmal hemicrania 3.2.2 Chronic paroxysmal hemicrania 3.3. Short-lasting unilateral neuralgiform headache attacks 3.3.1 Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) 3.3.1.1 Episodic SUNCT 3.3.1.2 Chronic SUNCT 3.3.2 Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) 3.3.2.1 Episodic SUNA 3.3.2.2 Chronic SUNA 3.4. Hemicrania continua 3.4.1 Hemicrania continua, remitting subtype 3.4.2 Hemicrania continua, unremitting subtype 3.5. Probable TACs 3.5.1 Probable cluster headache 3.5.2 Probable hemicrania continua 3.5.3 Probable short-lasting neuralgiform headache attacks 3.5.4 Probable hemicrania continua
4.	Other primary headaches

CH is a severe primary headache affecting 1/1000 people of the general population, as shown by a meta-analysis of 16 population-based studies conducted by Fischera et al. in 2008 (2). The most recent evidence on the epidemiology of CH comes from Ethiopia reporting a prevalence of 1.3% of the general population (3). CH's signature symptom is a one-sided severe pain, described by some authors as the most severe pain known to man (4). CH is characterized by attacks of unilateral pain associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis and/or eyelid oedema (see Figure 1.1), and/or with restlessness or agitation (5) (see Figure 1.2).

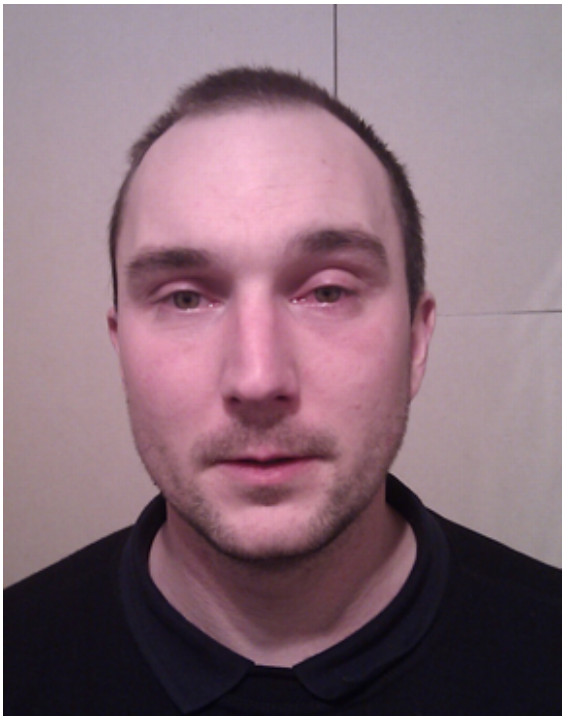


Figure 1.1. Cranial autonomic features during a CH attack. The image shows left periorbital oedema, left partial ptosis, left conjunctival injection and tear formation. The signs reverted to normal when the attack stopped. (Reproduced from Nesbitt AD, Goadsby PJ. Cluster headache. BMJ (Clinical research ed). 2012;344:e240 with permissions from BMJ Publishing Group Ltd.) (6)

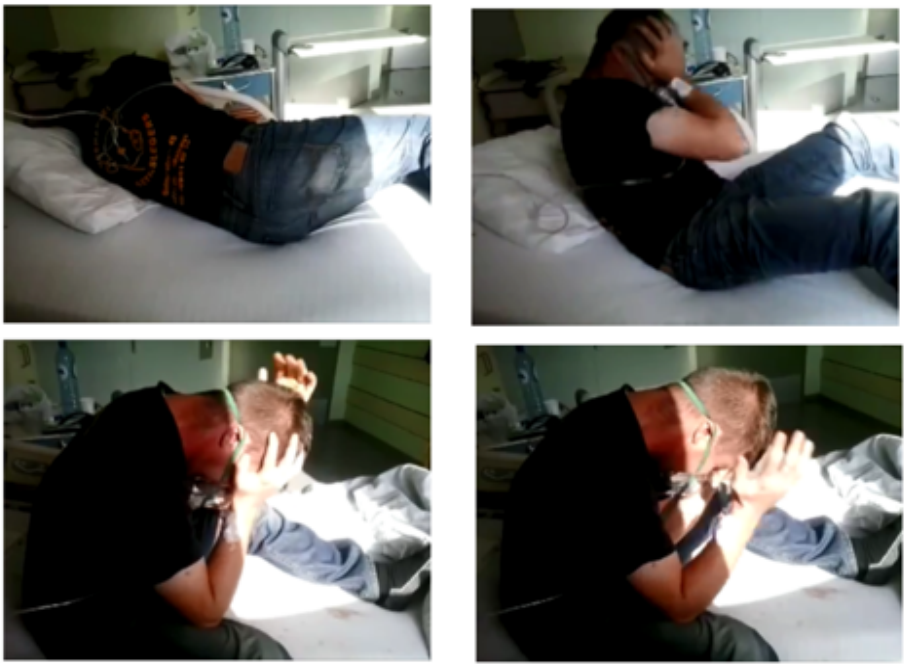


Figure 1.2. The restlessness associated with the CH attacks. The patient is treated with inhalation of oxygen during the attacks. (Reproduced with permissions from Dr Koen Paemeleire, Ghent University Hospital, Belgium)

The CH attacks can last between 15 min to three hours, occurring from every other day to eight times a day (1). ICHD-3 diagnostic criteria for CH is presented in Table 1.2 (1).

Table 1.2. The diagnostic criteria of CH (ICHD-3)

Clinical features	
A.	At least five attacks fulfilling criteria B–D
B.	Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes (when untreated)
C.	Either or both of the following:
	1. at least one of the following symptoms or signs, ipsilateral to the headache: a) conjunctival injection and/or lacrimation b) nasal congestion and/or rhinorrhoea c) eyelid oedema d) forehead and facial sweating e) miosis and/or ptosis 2. a sense of restlessness or agitation
D.	Attacks have a frequency between one every other day and eight per day for more than half of the time when the disorder is active
E	Not better accounted for by another ICHD-3 diagnosis

CH is maximal orbitally, supraorbitally, temporally or in any combination of these sites, but may spread to other regions (1). During the worst attacks, the intensity of pain is excruciating (7). Patients with CH, unlike those with migraine, are unable to lie down, and characteristically pace and rock back and forth (1). The period over which attacks recur is referred to as the cluster period (8). Pain usually recurs on the same side of the head during a single cluster period (9). CH tends to occur in bouts lasting for weeks or months separated by remission periods, which is the hallmark feature of the syndrome. There are two sub-types of cluster headache: episodic CH and chronic CH. Episodic CH is the most common type of CH and experienced by 85 to 90% of patients with CH (10). The cluster periods may vary from 1-2 weeks to 2-3 months and the interval between them vary from months to years (11). There is a preponderance in spring and autumn (1). Men are affected more than women (2). The male:female ratio varies from 5-6:1 (12, 13) or 8-9:1 (14, 15) to an estimated 2-3:1 according to more recent studies (4, 16, 17). Ten to 15% of patients with CH have chronic CH, which is

characterized by attacks occurring for more than one year without remission or remission lasting less than three months (9).

1.1.2 Management

CH management is unique compared to other primary headaches. Due to short lived attacks, CH is treated with nasal or parenteral triptans, including sumatriptan (18) or zolmitriptan (19). CH is the only primary headache for which oxygen is effective (20). Administration of oxygen delivered through non-rebreathing masks relieves the pain within 15 minutes in 78% of CH sufferers (21). Opioids and the non-steroidal anti-inflammatory medication are not effective in the acute management of CH (8). Short periods of CH are managed with short-term prevention with corticosteroids, although their use should be phased out due to the cumulative side effects of steroids (22-24). Administration of greater occipital nerve blocks is an alternative for patients with short bouts (25). Chronic CH or long periods of CH require long term preventative therapy. Verapamil, traditionally used for angina, arrhythmia or hypertension is the drug of choice (26). Lithium, second line treatment requires adequate monitoring of the renal and thyroid function (27). Due to the side effect profile and close monitoring requirements, the use of lithium is gradually declining (28). Only empirically used, topiramate, sodium valproate, pizotifen have no convincing evidence of efficacy (27). Recently, drugs against the calcitonin gene related peptide (CGRP) have been developed for the treatment of CH. Monoclonal antibodies against CGRP including galcanezumab and fremanezumab have been tested in CH, with moderate effect on episodic CH but failed to prove effective in chronic CH (29-31). Currently on the rise in the headache field, neuromodulation techniques such as non-invasive vagus nerve stimulation are recommended for both episodic and chronic CH (32, 33). Invasive therapies such as the sphenopalatine ganglion stimulation (34) and hypothalamic deep brain stimulation are reserved for refractory cases of CH (35).

1.2 Study objectives and research questions

The overarching aim of this doctoral research project is to explore the diagnosis of CH from different perspectives. Here, I outline two main study objectives:

(1) To identify the current knowledge on the challenges with the diagnosis of CH
(2) To investigate strategies for the early diagnosis of CH

Building on the study objectives, I aim to answer the following research questions:

(1) What is the current evidence on the time to correct diagnosis of CH?
(2) What is the most recent literature on the pathophysiology of CH and possible biological markers to aid the diagnosis?
(3) What type of screening instruments could facilitate the early diagnosis of CH?
(4) What are the perspectives and understandings of CH diagnosis among participants with CH and clinicians (GPs and neurologists)?

Table 1.3 presents the study flow consisting of the four workstreams in my doctoral research, as well as how I disseminated findings and results through presentations and peer-reviewed journal publications. I examined the diagnosis of CH through a multi-method strategy. Two literature reviews were conducted: (1) a systematic literature review on the delays in diagnosis and misdiagnosis of CH and (2) a literature review on the pathophysiology of CH. This was followed by both qualitative and quantitative research methods: (1) quantitative study approach including developing and investigating an innovative screening tool for the early detection of CH and (2) qualitative research exploring perceptions on the CH diagnosis from three stakeholders: participants with CH, GPs and neurologists.

Table 1.3. Study flow and thesis dissemination

STUDY OUTLINE	THESIS DISSEMINATION
PART I Systematic literature review on the delays in diagnosis and misdiagnosis of CH	**Articles** A. Buture, F. Ahmed F, L. Dikomitis, J.W. Boland. Systematic literature review on the delays in the diagnosis and misdiagnosis of cluster headache. *Neurol Sci.* 2019; 40(1):25-39; https://doi.org/10.1007/s10072-018-3598-5 (36) **Conference abstracts** A. Buture, F. Ahmed, L. Dikomitis and J.W. Boland. Misdiagnosis and physicians seen prior to the correct diagnosis of cluster headache: a systematic literature review. *Cephalalgia* 2019; Vol. 39(1S) page 57 A. Buture, J.W. Boland, L. Dikomitis and F. Ahmed. Delays in the diagnosis and misdiagnosis of cluster headache – a systematic literature review, *Cephalalgia* 2018; Vol. 38(1S) 1–115 **Poster presentations** Misdiagnosis and physicians seen prior to the correct diagnosis of cluster headache: a systematic literature review. The International Headache Society Congress, Dublin 2019 Delays in the diagnosis and misdiagnosis of cluster headache – a systematic literature review, 17th biennial Migraine Trust International Symposium (MTIS), London 2018
PART II Literature review on the pathophysiology of CH	**Articles** A. Buture, J.W Boland, L. Dikomitis, F. Ahmed. Update on the pathophysiology of cluster headache: imaging and neuropeptide studies. *J Pain Res.* 2019; 12 269–281; https://doi.org/10.2147/JPR.S175312 (37)

STUDY OUTLINE	THESIS DISSEMINATION
PART III Prospective observational study to evaluate a novel screening tool for CH **Phase I: Screening tool development** **Phase II: Pilot study** The screening tool was tested on patients with CH and migraine (control group) and refined based on their feedback **Phase III: Larger-scale study** The screening tool assessed on patients with CH and migraine (control group)	**Articles** A. Buture, J.W. Boland, L Dikomitis, C Huang, F Ahmed. Development and evaluation of a screening tool to aid the diagnosis of cluster headache. *Brain Sci.* 2020; 10, 77; https://doi.org/10.3390/brainsci10020077 (38) A. Buture, J.W. Boland, F Ahmed, L Dikomitis. Images depicting headache pain - a tool to aid the diagnosis of cluster headache-a pilot study. *Journal of Multidisciplinary Healthcare* 2019;12 691–698; https://doi.org/10.2147/JMDH.S207128 (39) **Conference abstracts** A. Buture, L. Dikomitis, J.W. Boland and F Ahmed. A literature review of screening tools for the detection of cluster headache. *Cephalalgia* 2019; Vol. 39(1S) page 47 A. Buture, J.W. Boland, F. Ahmed and L. Dikomitis. Images portraying headache pain – a tool to aid the diagnosis of cluster headache. *Cephalalgia* 2019; Vol. 39(1S) page 59 A. Buture, L. Dikomitis, J.W. Boland and F. Ahmed. Images depicting pain – a screening tool for cluster headache, *Cephalalgia* 2018; Vol. 38(1S) 1–115 A. Buture, L. Dikomitis, J.W. Boland and F. Ahmed. Visual Images – an additional tool for the screening of cluster headache, *Cephalalgia* 2017; Vol. 37(1S) 1–24 A. Buture, L. Dikomitis, F. Ahmed. Developing a diagnostic tool for the early diagnosis of cluster headache, *Cephalalgia* 2016; Vol. 36(1S) 1–185 **Presentations** **Oral presentations** Diagnosing cluster headache, Head Start meeting, London 2019 Cluster headache. How we diagnose and what can we improve? Migraine Trust Public Meeting, Hull 2019

Delays in the diagnosis of trigeminal autonomic cephalalgias. How can we improve? The British Association for the Study of Headaches (BASH) meeting, Hull 2017

Poster presentations

Images portraying headache pain – a tool to aid the diagnosis of cluster headache. The International Headache Society Congress, Dublin 2019

A literature review of screening tools for the detection of cluster headache. The International Headache Society Congress, Dublin 2019

Images depicting pain – a screening tool for cluster headache, 17th biennial Migraine Trust International Symposium (MTIS), London 2018

Visual Images – an additional tool in the diagnosis of cluster headache, The International Headache Society Congress, Vancouver, Canada 2017

Visual Images – an additional tool in the diagnosis of cluster headache, International Headache Academy (iHEAD) Meeting, Vancouver, Canada 2017

Developing a diagnostic tool to aid early diagnosis of cluster headache, Hull York Medical School Conference, Hull 2017

Developing a diagnostic tool for the early diagnosis of cluster headache, The 5th European Headache and Migraine Trust International Congress – EHMTIC, Glasgow 2016

A new diagnostic tool for the early diagnosis of cluster headache, International Headache Academy (iHEAD) Meeting, London 2016

Developing a diagnostic tool to aid early diagnosis of cluster headache, Hull and York Medical School Conference, York 2016

PART IV	Articles
Qualitative study to explore the perceptions on the CH diagnosis among three stakeholders: participants with CH, GPs and neurologists	A. Buture, F. Ahmed, Y. Mehta, K. Paemeleire, P.J. Goadsby, L. Dikomitis. The perceptions and experiences of cluster headache among GPs and neurologists: a qualitative study. *Br J Gen Pract,* 2020; 70 (696): e514-e522; https://doi.org/10.3399/bjgp20X710417 (40)
	Dissemination to the general public
	L. Dikomitis, A. Buture, F. Ahmed. Cluster headache is more than 'just a headache' but this excruciating condition is often misdiagnosed. The Conversation. June 2020. https://theconversation.com/cluster-headache-is-more-than-just-a-headache-but-this-excruciating-condition-is-often-misdiagnosed-139700

CHAPTER 2. SYSTEMATIC LITERATURE REVIEW ON THE DELAYS IN DIAGNOSIS AND MISDIAGNOSIS OF CLUSTER HEADACHE

2.1 Introduction

There is increasing evidence that patients with CH suffer for many years before receiving a correct diagnosis (41). As a consequence, they consult many clinicians and receive inappropriate treatments (42). A robust literature review that focuses on the delays in the diagnosis and misdiagnosis of CH has not yet been conducted. In this chapter, I explore the diagnostic delays and under-recognition of CH by conducting a systematic literature review. The review focused on multiple variables: length of time to correct diagnosis of CH, diagnosis received prior to CH diagnosis, the type and number of clinicians seen prior to diagnosis, treatment received prior to diagnosis and factors involved in the diagnostic delay. I also explore possible contributors to delays in diagnosis, misdiagnosis and mismanagement of CH.

2.2 Aim and objectives

The aim of this systematic literature review is to identify, appraise and synthesise all relevant clinical studies on the misdiagnosis and delays in the diagnosis of CH.

2.3 Methods

The systematic review was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols (PRISMA-P) 2015 guidelines (43) and was conducted and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (44). It was registered with International Prospective Register of Systematic Reviews (PROSPERO) on 9/11/2017 (registration number: CRD42017081204).

2.3.1 Search strategy

A comprehensive search of different electronic databases was carried out in May 2017 to identify potential studies. The following electronic databases were searched: Medline,

EMBASE, PsycINFO, PubMed, CINAHL, BNI, HMIC, AMED, HBE (NICE Healthcare Databases) and Cochrane Library. Pre-specified search criteria were designed with input from a professional librarian search specialist, Medical Subject Heading and free text terms were used to increase the search sensitivity.

To search for misdiagnosis the search terms were: misdiagnosis OR diagnostic error OR hidden diagnosis OR unrecognised diagnosis OR alternate diagnosis OR undiagnosed OR diagnostic mistake OR missed diagnosis. The search terms for delays in diagnosis were: delays in diagnosis OR late diagnosis OR delayed diagnosis. These were combined with a search for cluster headache OR cluster-like headache. In addition to the electronic search, I screened the reference lists of the included articles and relevant literature known by the authors. The detailed search criteria are presented in Appendix 1.

Two reviewers (AB and JB) independently assessed all titles and abstracts for inclusion. The inclusion/exclusion criteria implemented for all searches are shown in Table 2.1.

Table 2.1. Inclusion and exclusion criteria

Inclusion	**Exclusion**
Study design	
Prospective and retrospective studies, case series and survey studies on misdiagnosis and/or delays in the diagnosis of CH	Case reports
Participants	
Children or adult patients with a diagnosis of CH according to ICHD criteria confirmed by a neurologist	Children or adult patients with a diagnosis of CH not based on ICHD criteria and not confirmed by a neurologist; Studies with less than 10 participants
Date	
There will be no restrictions by date	
Geographical location	
There will be no restrictions by geographical location	
Language	
There will be no restrictions by language. Non-English language articles will be included and all the foreign language articles will be translated. However, if the translation is not possible, it will be recorded	

Full text papers were retrieved for those meeting the inclusion criteria and for those articles whose eligibility criteria could not be assessed based only on the title and abstract. Two reviewers (AB and JB) independently assessed all full text articles and disagreement was resolved by discussion to reach consensus and if needed with the intervention of a third reviewer (FA). The findings are reported according to PRISMA guidelines (44).

2.3.2 Data extraction, assessment and analysis

The data was independently extracted by two reviewers (AB and JB). Data extracted included: the study design, methods of data acquisition, study population (number of participants, male:female ratio, percentage of patients with episodic and chronic CH, time from disease onset to diagnosis (the patients' delay: the mean time between the CH attack and first consultation of a clinician, clinicians' delay: the mean time between the first consultation of a clinician and correct diagnosis and the mean total delay: sum of patients' delay and clinicians' delay), percentage of patients misdiagnosed, diagnosis received prior to CH diagnosis, the type and number of clinicians seen prior to diagnosis, treatment received prior to diagnosis and factors involved in the diagnostic delay. The discrepancies were resolved through discussion with a third reviewer (FA).

2.3.3 Quality assessment of the included studies

The risk of bias in individual studies was conducted in order to assess the quality of the studies included in the SLR. Quality assessment was performed using The Joanna Briggs Institute (JBI) Appraisal Checklist for case series studies (see Appendix 2) (45). Ten domains of the study design and reporting were assessed, each rated 'Yes', 'No', 'Unclear' or 'Not applicable'. The Oxford Centre for Evidence Based Medicine (OCEBM) Critical Appraisal was used for survey studies (see Appendix 3) (46). Ten domains of the study design and reporting were assessed, each rated 'Yes', 'No', 'Unclear 'or 'Not applicable'. Studies were not excluded based on their quality appraisal. The studies were independently assessed by two reviewers (AB and JB) and the discrepancies were resolved through discussion with a third reviewer (FA).

2.4 Results

In this section, I present data on the study's characteristics and participants' profile and I continue with details on non-English articles and the quality assessment of the studies included in this systematic literature review. I further present results on delays in diagnosis, misdiagnosis and clinicians seen prior to correct diagnosis and mismanagement. I conclude this section with factors that contributed to delayed and missed diagnosis.

2.4.1 Study characteristics

The search carried out in May 2017 on diagnostic delays and misdiagnosis of CH identified 201 unique studies. The retrieved articles were published between January 1978 and May 2017. All studies were screened by title and abstract and 149 articles were excluded at this stage. Full text articles were assessed for the remaining 52 studies and 15 studies met the inclusion criteria. Thirty-seven articles were excluded after the full text screening. The reasons for exclusion are shown in the PRISMA flow chart (see Figure 2.1). The 15 included studies took place in Europe, USA and Asia. Four studies were from USA, three from Denmark, one each from Greece, Serbia, Spain, Norway, Japan, Britain, and Belgium. One study was conducted in multiple countries: Italy, Moldova, Ukraine and Bulgaria. Thirteen case series studies and two survey studies were included. Nine studies assessed both the delays in diagnosis and misdiagnosis of CH, five studies the delays in diagnosis and one study the misdiagnosis of CH.

ELECTRONIC DATABASES	RESULTS
EMBASE	138
MEDLINE	67
PUBMED	104
Psych INFO	20
Cochrane Library	1
HBE	1
HMIC	0
AMED	0
CINAHL	1
BNI	1

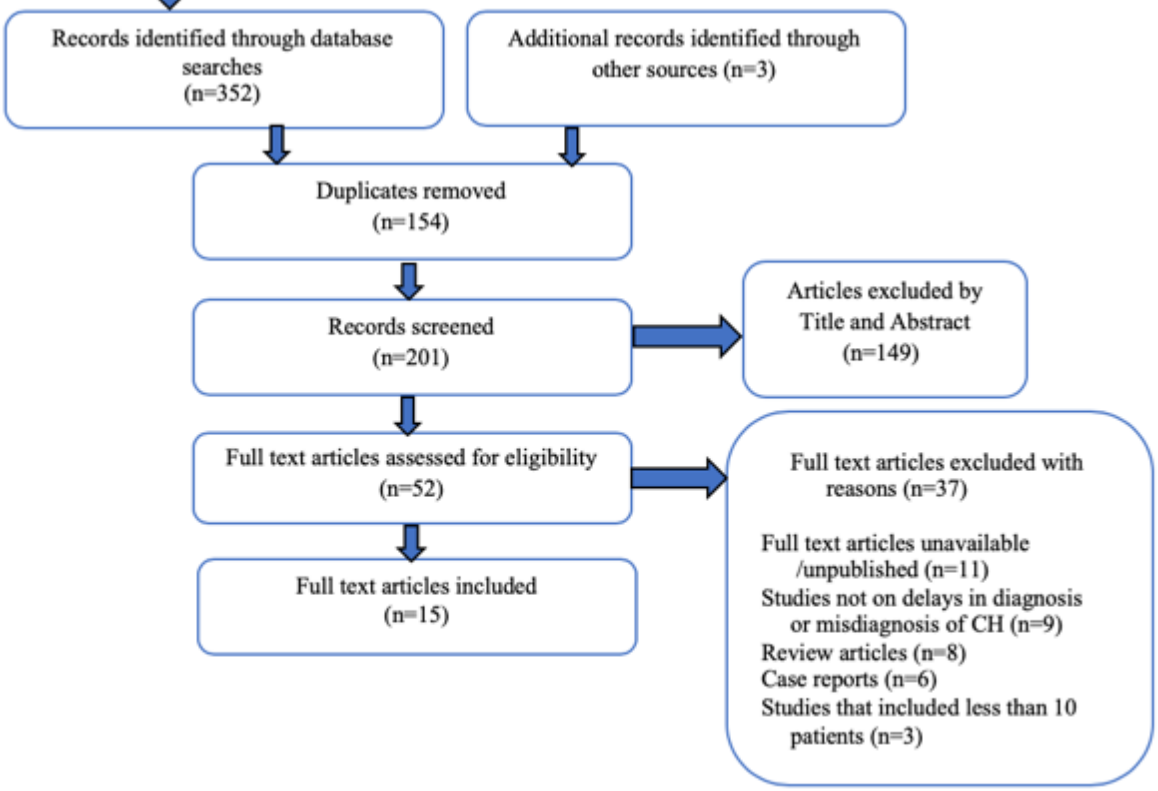


Figure 2.1. PRISMA Flow diagram of study selection based on Preferred Reporting Items for Systematic Review and Meta-analysis protocol

Abbreviations: CINAHL: Cumulative Index to Nursing and Allied Health Literature; BNI: British Nursing Index; HMIC: Health Management Information Consortium; AMED: Allied and Complementary Medicine Database; HBE: Health Business Elite

The data extracted from case series and survey studies is shown in Table 2.2 and Table 2.3. The values in Table 2.2 and Table 2.3 are extracted from the original (referenced) papers and the percentage values are rounded to the nearest integer. The number of patients with episodic CH and chronic CH were converted into percentages where necessary for consistency. The ratio (male: female) was calculated if it was not provided in the cited work.

2.4.2 Participants' characteristics

The studies included a total of 4661 patients, aged 3-81 years, men and women with episodic CH and chronic CH. The percentage of patients with episodic CH varied from 64 to 100%. The male to female ratio varied from 1.9:1 (17) to 9.6:1 (14). One included study was in children with CH (13).

2.4.3 Non-English articles

Four full text articles in foreign languages were identified and translated using online translation tools (google translate) (47-50). The articles were excluded as they did not meet the inclusion criteria (the studies were not on delays in diagnosis or misdiagnosis of CH).

Table 2.2. Data extracted from case series and survey studies

Country	Author	Number of patients and male:female ratio (R)	Study design	Methods of data acquisition	ECH CCH (%)	Time from disease onset to correct diagnosis (years)	Misdiagnosis and percentage of patients misdiagnosed (%)	Types of clinicians seen prior to diagnosis	Treatment received prior to diagnosis
Denmark	Lund et al. 2017	351 R = 2:1	Retrospective study	362-item questionnaire and structured interview	64 ECH 36 CCH	Mean total delay 6.2 total group 6.56 men 5.50 women	Migraine 25% TTH 19% Sinusitis 14% 61% women; 46% men misdiagnosed	NR	NR
Greece	Vikelis & Rapoport 2016	302 R=3,6:1	Retrospective study	Semi-structured questionnaire and neurological examination	78 ECH 22 CCH	Median total delay (range) <1989: 20 (0-45) 1990-1999: 12 (2-21) 2000-2009: 5 (0-14) 2010-2015: 1 (0-7)	Migraine 51% Trigeminal neuralgia 42% Ophthalmic disease 11% Dental or jaw disease 15% ENT disease 25% Cervical spine disease 12%	GP 65% Dentist 26% ENT specialist 36% Ophthalmologist 31% Neurologist 41% Neurosurgeon 9% Other 23% Self-diagnosis 13%	Pharmaceutical treatment 63% Unnecessary Procedures 14% Dentists 10% ENT 10%
Serbia	Zidverc-Trajcovic et al. 2014	182 R=1,9:1	Retrospective case series	Clinical note review	89 ECH 11 CCH	Mean total delay 7.8 ± 8.0 (whole group) <20 years age of onset (13.8± 9.7) 20-40 years age of onset (7.9± 7.6) >40 years age of onset (4.2± 2.1) 69% of patients had a diagnostic delay longer than two years	NR	NR	NR

Italy Moldova Ukraine Bulgaria	Voiticovski - Iosob et al. 2014	144 R=2,7:1	Consecutive case series	Clinical examination (74%) and 20-item questionnaire delivered over the phone (26%)	100 ECH	Mean total delay 5.3 ± 6.4 (range 0-30) Eastern European countries: 4.0±3.7 Italy: 5.6± 6.9 Patient delay 24% (did not seek medical advice)	Trigeminal neuralgia 29% Migraine without aura 23% Sinusitis 17% Headache attributed to idiopathic intracranial hypertension 6% TTH 6% Dental problems 4% Depression 4% Questionable CH 3% Self-diagnosis 15% 77%patients misdiagnosed	Neurologists 49% General practitioners 35% ENT specialists 10% Dentist 3% Other 4% (Ophthalmologist, Paediatrician, Anesthesiologist, Cardiologist, Emergency medicine) 2.6 clinicians/ patient	131/144 Symptomatic treatment 91% (of these: triptans 17%, oxygen 1%, NSAIDS 55%, Combination of analgesics 18% 33/144 Preventative medication 23% 44/144 Non-pharmacological treatment 31% (of these: acupuncture 32%; Physical therapy 16%; Relaxation techniques 11%; Cold therapy 9%; Tooth extraction 16%; Sinus medications aerosol 2%; Other drugs cannabis, marijuana, alcohol 9%, homeopathy, chirotherapy 5%)
Spain	Sanchez del Rio et al. 2014	75 R=8,3:1	Consecutive case series	10-item questionnaire study	NR	Mean total delay 4.9 (range 1month-28)	Migraine 45% No diagnosis 28% Trigeminal neuralgia 25% Sinusitis 19% Dental pain/jaw disease 16% Psychiatric 9% SUNCT 3% 57 % patients misdiagnosed; 28% no specific diagnosis	4.6 clinicians/ patient (range 1-12)	60% of patients received inappropriate treatment
Norway	Bekkelund et al. 2014	70 R:4,8:1	Patients identified in the registers of two neurological departments	Questionnaire and diagnosis confirmed through clinical chart or over the phone	NR	Median total delay 4 (range 0-30)	NR	NR	Acupuncture 29% Chirotherapy 19% Physiotherapy 1% Cannabis 1% Naprapathic treatment 1% Healing 1% Scuba diving 1% Reflexology 1% Dental treatment 1%

USA	Rozen & Fishman 2012	1134 R=3,8:1	Nationwide survey study	187-item questionnaire (website based)	NR	Total delay-percentage: <1yr (25%); 1 yr (7%); 2yrs (10%); 3yrs (9%); 4yrs (6%); 5yrs (7%) 6yrs (4%); 7yrs (4%) 8yrs (4%); 9yrs (2%) 10+ (22%) >5 years in 42% patients	Migraine 34% Sinusitis 21% Allergies 6% Tooth-related issues 5%	NR	NR
Japan	Imai et al. 2010	86 R=3,8:1	Consecutive case series	Structured interview	96 ECH 4 CCH	Mean total delay 7.3±6.9 years (range 0-28)	NR	NR	NR
Belgium	Van Alboom et al. 2009	85 R =9,6:1	Consecutive case series	Self administered 90- item questionnaire	79 ECH 21 CCH	Mean total delay 44mts Physician's delay Mean 35mts Patient's delay Mean 11mts <1yr (54%) 2-4yrs (14%) 5-10yrs (18%) 10+yrs (13%)	Migraine 45% Sinusitis 23% Tooth/jaw problem 23% TTH 16% Trigeminal neuralgia 16% Ocular problems 10% Neck/back disorders 7% Nasal disorders 5% 65% patients misdiagnosed	NR	Non-specific analgesia (79%) 46/85 Invasive therapy (of these: dental procedures 21%; Sinus surgery 10%) Inappropriate preventative treatments (Carbamazepine 12%; Propranolol 12%; Amitriptyline 9%) 40/85 Alternative therapies 47% (of these: Acupuncture 26%; Osteopathy 18%; Chiropractics 15%; Homeopathy 13%; Herbal therapy 11%; Spiritual healing 7%; Reflexology 6%; Hypnosis 2%)
Denmark	Jensen 2007	85 R:1,9:1	Case series study	Semi-structured 97 question telephone interview and clinical note review	79 ECH 20 CCH 1 UND	Mean total delay 9 (range 0–39) whole group ECH: 8 (range 0-35) CCH 9 (range 0-39)	NR	44.7% (38/85) of patients had previously been admitted to hospital due to CH	Non-medical treatment was received by 58% (49/85)
UK	Bahra & Goadsby 2004	230 R: 2,5:1	Case series study (24%) and patients recruited from national support groups (76%)	Interview and questionnaire (telephone or face-to-face)	ECH 79 CCH 21	Mean total delay Before 1950 (12yrs) 1950-1959 (22.3yrs) 1960-1969 (17.2yrs) 1970-1979 (9.5yrs) 1980-1989 (6.4yrs) 1990-1999 (2.6yrs)	NR	Dentist 45% ENT specialist 27% Optician 32% Ophthalmologist 15% Other: physician, migraine clinic, neurosurgeon, psychiatrist, pain clinic7% Self-diagnosis 13%	Tooth extraction, splint, brace, filling, X-rays, maxillo-facial surgery 18% Sinus washout, surgery for nasal septum deviation, antibiotics, X-rays 13% Spectacle prescription altered, eye-exercises 3%

Netherlands	Van Vliet et al. 2003	1163 R: 3,7:1.	National mailing via headache groups, GPs, neurologists	Questionnaire	73 ECH 21 CCH 6 UND	Median total delay 3yrs (range 1w-48yrs)	Sinusitis 21% Migraine 17% Dental-related pain 11%	Dentists 34% ENT specialists 33% Alternative therapists 33%	Tooth extraction 16% ENT operation 12%
USA	Klapper et al. 2000	686	Patients accessing CH website were invited to participate in an internet survey	28-item questionnaire	85 ECH 15 CCH	Mean total delay 6.6 years	3.9 (average number of incorrect diagnoses)	4.3 clinicians/ patient (average)	NR
USA	Maytal et al. 1992	35 R: 6:1	Case series study	Semi-structured interviews	86 ECH 14 CCH	Mean total delay 8.5 (range 0-34)	NR	Neurologists or headache specialists 71% Internists or general practitioners 37% Otolaryngologists 26% Pediatricians 26% Ophthalmologists 23% Psychiatrists 11% Chiropractors 6% Orthopaedic surgeons 3% Allergists 3%	Surgical repair of a deviated septum (1)
USA	Bittar &Graff-Radford 1992	33 R: 3:1	Retrospective consecutive case series	Clinical note review	NR	NR	NR	NR	Headache compounds (Fiorinal, Fioricet, Cafergot, Midrin) NSAIDS (Aspirin, Dolobid, Motrin) Membrane stabilizing drugs (Tegretol, Dilantin, Lioresal) Narcotics (Dilaudid, codeine, MS Contin) Tricyclic antidepressants Dental procedures (Oral orthosis18%; Teeth extracted 12%; Coronoplasty 9%, Root canal treatments 6%)

Abbreviations: ECH: episodic cluster headache; CCH: chronic cluster headache; GP: general practitioner; TTH: tension-type headache; ENT: ear-nose-throat; UND: undetermined; NR: not recorded; R: male:female ratio

Table 2.3. Factors involved in diagnostic delays

Vikelis and Rapoport 2006			Van Vliet et al. 2003			Van Alboom et al. 2009	
Parameter	**Years to diagnosis median (range)**	**p-value**	**Parameter (% of patients)**	**Years to diagnosis Median (range)**	**p-value**	**Parameter**	**p-value**
Decade of onset		**0.001**	Episodic CH (73%)		**0.001**	Lower age at onset	
<2000 2000-2009 >2010	13 (0-45) 5 (0-14) 1 (0-7)		No Yes	1 (<1–28) 3(<1–48)		Pain that does not reach the peak within the first five minutes	p<0.05
Side shift between bouts		**0.008**	Nausea during attacks (27%)		**0.001**		
No Yes	5 (0-45) 8 (0-26)		No Yes	2.3 (<1–48) 4 (<1–45)			
Jaw location of pain		**0.002**	Vomiting during attacks (12%)		**0.003**		
No Yes	5 (0-30) 7 (0-45)		No Yes	2.5 (<1–48) 4.8 (<1–37)			
Cheek location of pain		0.015	Photophobia/phonophobia (54%)		0.022		
No Yes	5 (0-30) 7 (0-45)		No Yes	2 (<1–48) 3 (<1–48)			
Lower teeth location of pain		0.015	Nocturnal onset of attacks (78%)		**0.009**		
No Yes	5 (0-30) 10 (0-45)		No Yes	2 (<1–35) 3 (<1–4)			
Ear location of pain		0.041	Interictal headache (16%)		0.078		
No Yes	5 (0-41) 10 (0-45)		No Yes	3 (<1–48) 2 (<1–42)			
Photophobia		0.016	Circadian rhythm (64%)		0.459		
No Yes	4 (0-30) 6 (0-45)		No Yes	2 .5 (<1–40) 3 (<1–48)			
Aggravation by physical activity		**0.008**	Restlessness (76%)		0.797		
No Yes	3 (0-20) 6 (0-45)		No Yes	2 (<1–37) 3 (<1–48)			
Forehead and facial sweating		0.018	Pain radiating to jaw (37%)		0.387		
No	5 (0-30)		No	2.5 (<1–48)			

Yes	6 (0-45)	Yes	3 (<1–42)	
Absence of autonomic features	0.023	Alternating attack side (11%)	**0.001**	
No Yes	2 (0-14) 5 (0-45)	No Yes	2.5 (<1–48) 6 (<1–34)	

Note: the statistical significance was set at $p<0.05$ (parameters with $p<0.05$ are highlighted in bold)

2.4.4 Quality assessment of the included studies

Two appraisal checklist tools were used to assess the quality of the studies included in this review. JBI Appraisal checklist was utilised for case series and OCEBM Critical Appraisal of a Survey for survey studies. The 13 case series assessed using JBI Appraisal Checklist were consecutive case series (13-15, 51-53) and non-consecutive case series (16, 42, 54), as well as retrospective case series (12, 17) (55) (see Table 2.4). Two survey studies were assessed using the OCEBM Critical Appraisal of a Survey (see Table 2.5). All studies had clear reporting of the demographics of the participants, except one study conducted by Klapper et al. (56). This internet-based questionnaire study included 798 participants (76% men; 28% women) of which 87% met the criteria for CH but the percentage of men and women that met the criteria for CH was not reported (56). Four studies included in this systematic review did not report the percentage of patients with episodic and chronic CH enrolled (12, 15, 55, 57). The data acquisition was unclear in ten out of 15 studies (12, 14-16, 41, 42, 51, 54, 56, 57). Only one study reported the questionnaire utilised for data acquisition (56). Five studies out of 15 assessed the statistical significance of the results (14, 16, 17, 51, 54), whereas in the other studies is lacking. Studies were not excluded if they did not assess all the variables established for data extraction. For example, only three studies reported the factors involved in diagnostic delays and misdiagnosis of CH. Although some studies assessed the length of diagnostic delays, the type of incorrect diagnoses was not captured (12, 13, 17, 42, 53, 56). Other studies did not report the type of clinicians seen prior to correct diagnosis of CH (12, 14, 16, 17, 52, 55, 57). Studies were not excluded based on their quality appraisal.

Table 2.4. Critical appraisal of case series using the JBI appraisal tool

Author	Were there clear criteria for inclusion?	Was the condition measured in a standard, reliable way for all participants?	Were valid methods used for identification of the condition for all participants included?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting in the demographics of the participants?	Where there clear reporting of clinical information of the participants?	Were the outcomes or follow up results of cases clearly reported?	Was there clear reporting in the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?
Lund et al. 2017	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Vikelis & Rapoport 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zidverc-Trajcovic et al 2014	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Voiticovski-Iosob et al. 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sanchez del Rio et al. 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bekkelund et al 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Imai et al. 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Van Alboom et. al 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jensen 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bahra & Goadsby 2004	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes

Van Vliet et. al 2003	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Maytal et al 1992	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bittar-Graff Radford 1992	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

Table 2.5. Critical appraisal of survey studies using the OCEBM appraisal tool

Author	Did the study address a clearly focused question?	Is the study design appropriate for answering the research question?	Is the method of selection of subjects clearly described?	Could the way the sample was obtained introduce selection bias?	Was the sample of subjects representative with regard to the population to which the findings will be referred?	Was the sample size based on pre-study consideration of statistical power?	Was a satisfactory response rate achieved?	Are the measurements likely to be valid and reliable?	Was the statistical significance assessed?	Are the CI given for the main results?	Could there be confounding factors that have not been accounted for?	Can the results be applied to your centre?
Rozen& Fisherman 2012	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No	Yes
Klapper et al. 2000	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No	Yes

Abbreviation: CI: confidence interval

2.4.5 Diagnostic delays

Fourteen of the 15 studies investigated the total delay in diagnosis (e.g. the time from disease onset to correct diagnosis). The studies reported different statistics for the time to correct diagnosis (mean, median or percentage). Ten studies assessed the mean time to correct diagnosis (13-17, 41, 42, 52, 53, 56), three studies the median time (12, 51, 54) and one study the percentage of patients that experienced delays in diagnosis (57). The mean time to correct diagnosis recorded in the UK was 2.6 years (between 1990-1999) (42), in Belgium 3.6 years (14), in Spain 4.9 years (15), in Italy and East European countries 5.3±6.4 years (quoted verbatim form the original paper) (41), in Denmark between 6.2 years (16) and 9 years (53), in USA between 6.6 (56) and 8.5 years (13), in Japan 7.3±6.9 years (52) and in Serbia 7.8±8 years (quoted verbatim form the original paper) (17). The median time to correct diagnosis was 1 year (range 0-7) in Greece (51), 3 years (range 1-48) in Denmark (54) and 4 years (range 0-30) in Norway (12). In one study performed in the USA, 42% of patients waited more than 5 years to receive a correct diagnosis of CH (57). Two studies showed a reduction in delay in the diagnosis of CH over time, from 22.3 years (before 1959) to 2.6 years (between 1990-1999) in UK (42) and from 20 years (prior to 1989) to 1 year (between 2010-2015) in Greece (51). Three studies explored both patients' and clinicians' delays in the diagnosis of CH (14, 41). Van Alboom et al. showed that the mean time between the first CH attack and the first consultation was 11 months (14) and Voiticovski-Iosob et al. found patients' delay in almost one quarter of cases (41).

While Bahra and Goadsby found no significant difference in time to diagnosis between men and women (42), Lund et al. showed that men waited a mean time of 6.5 years and women waited 5.5 years (16). Gender difference was also recorded by Vikelis and Rapoport where a median of 0 years (range 0-6) was found for men and 3 years (range 0-7) for women (51). One study assessed the influence of age of onset on the diagnostic delay (17). Zidverc-Trajkovic et al. showed that the condition is less recognised in patients with early onset of CH (less than 20 years of age) (17). People with late onset of CH (>40 years of age) were more rapidly diagnosed than subjects with typical age of onset of CH (20-40 years of age) (17). In the study conducted by Van Vliet et al. the patients with episodic CH had longer delays in diagnosis compared to chronic CH patients (54), probably due to longer remission periods.

2.4.6 Misdiagnoses

Migraine, trigeminal neuralgia, sinusitis and dental/jaw disease are the most common misdiagnoses. Other diagnoses received by the CH patients were: TTH, ophthalmic disease, ear nose and throat (ENT) disease, cervical spine disease, idiopathic intracranial hypertension, allergies, SUNCT and psychiatric disorders. Migraine was the most received misdiagnosis (14, 15, 51) followed by trigeminal neuralgia, (15, 41, 51). Sinusitis was often diagnosed in patients with CH, most likely due to presence of rhinorrhoea, nasal congestion and seasonal variation, although there was no significant statistical correlation between these features and the diagnosis of CH (14). The mean number of diagnosis received per patient in Italy and Eastern Europe was 2.2 (41), 3.9 in the USA (56). In Belgium, 65% of the patients studied were misdiagnosed (14) while in Italy and East Europe misdiagnosis was recorded in 77% of cases (41). In Denmark more women (61%) were misdiagnosed as migraine compared to men (45.5%) (16).

2.4.7 Mismanagement

Dentists and ENT specialists performed tooth extractions, fillings, sinus washout, surgery for nasal septum deviation without any success. Dentists, ENT specialists or other clinicians that did not recognise the disorder often recommended unnecessary investigations (MRI head, CT head, EEG, cervical spine X-ray, skull X-ray) to diagnose a secondary headache (41). Patients underwent alternative medicine treatments such as acupuncture (12, 14, 41, 55), homeotherapy (41), chirotherapy (12, 41, 55), relaxation techniques (41), cold therapy (41), reflexology (14), hypnosis (14), osteopathy (14), spiritual healing (14) and illicit drug use (12, 41). Even after obtaining a correct diagnosis of CH, patients complained of lack of information regarding the cause of the disorder and available treatments (15). Some patients received incorrect information as to the cause of CH (psychiatric, vascular disorder, genetic/familial, brain injury, alcohol, tobacco) and others received no information (15). Even general neurologists occasionally offered non-evidence based treatments for CH (13, 41, 51).

2.4.8 Clinicians seen prior to correct diagnosis

Patients with CH were often seen by different clinicians before the correct diagnosis was established. Vikelis and Rapoport showed that nearly two thirds of their Greek patients (63.5%)

consulted a general practitioner or internist, around one third an ENT specialist, ophthalmologist or dentist, and a small proportion (8.5%) a neurosurgeon (51). Forty-percent of patients in this study were seen by neurologists who missed the diagnosis (51). In Belgium, neurologists correctly diagnosed 80% of cases (14). Patients often sought help from alternative medicine specialists (acupuncturists and chiropractors) (12, 14, 41, 55). Even children consulted many different specialists prior to diagnosis (internists, general practitioners, otolaryngologists, ophthalmologists, psychiatrists, chiropractors, orthopaedic surgeons and allergists) (13). Self-diagnosis using different sources of information (internet, reading about CH and discussion with other people suffering with CH) with subsequent medical confirmation was the second most common way of diagnosis after clinicians' diagnosis (51). Self-diagnosis was reported in 4%, 13% and 15% of patients in Belgium (14), UK (42) and Italy and East European countries respectively (41). Patients consulted between 2-5 clinicians before the correct diagnosis was made (14, 15, 41, 51) frequently including a dentist, ENT specialists or ophthalmologist who exceptionally made the diagnosis (14). Vikelis and Rapoport found that patients with chronic CH consulted more clinicians than patients with episodic CH (median 4 versus 2) (51) and no differences in the number of clinicians consulted by men and women were found (51). Most patients with CH did not present to the emergency departments (57). The most obvious explanation would be the short duration of CH attacks.

2.4.9 Factors involved in diagnostic delay

Three studies assessed the factors involved in the diagnostic delay (14, 51, 54). Van Vliet et al. showed that the presence of episodic CH, nausea, vomiting during attacks, photophobia or phonophobia, nocturnal onset of attacks, restlessness, pain radiating to the jaw, alternating attack side and circadian timing of attacks delayed the diagnosis of CH (54). The male gender and interictal headache did not influence the correct diagnosis of CH (54). However, Vikelis and Rapoport showed that the side shift between bouts, aggravation by physical activity, the presence of forehead and facial sweating, the presence of photophobia and the absence of cranial autonomic features, the pain located in the jaw, cheek, lower teeth and ear delayed the correct diagnosis of CH (51). The authors have also shown that the decade of onset of CH influenced the correct diagnosis (51). Patients with onset before year 2000 waited a median of 13 years (range 0-45) to be diagnosed compared to patients with onset after year 2010 who waited a median of 1 year (range 1-7) (51). A lower age of onset and pain that does not reach

the maximum intensity within the first five minutes were also features that contributed to diagnostic delay (14).

2.5 Discussion

It is evident from the studies included in this review that diagnostic delay and misdiagnosis of CH is not limited to a geographical area. Although some countries had less delay than others, delays in diagnosis were recorded in multiple countries around the globe. Here, I discuss the delays in diagnosis, misdiagnosis, mismanagement of CH and factors involved in the diagnostic delays identified in this systematic literature review.

2.5.1 Delays in diagnosis

In the absence of a diagnostic biological marker, the diagnosis of CH relies on the clinicians' skills and knowledge to obtain a thorough clinical history based on the diagnostic criteria (1). Studies included in this review showed both patients' and clinicians' delay (14, 41). The reason why some patients with CH do not seek timely medical advice is not well understood. The short duration of the attacks could be an explanation although there are currently no studies that assessed this. As previously shown, patients who did not seek medical assistance for headache had more TTH, lower headache intensity and frequency, less migraine with aura or had relief from painkillers (58). It has been shown that the episodic pattern of attacks, a specific feature of CH, does not seem to contribute to an earlier diagnosis (54). Moreover, extended periods of remissions only prolong the time to correct diagnosis (14, 15, 54). Improved awareness of the condition is the most probable reason for the reduction of time to correct diagnosis in the UK, Greece and Denmark (16, 42, 51, 53). In addition, a better access to specialised neurological centres and a better education of medical students may have improved clinicians' delay (42). Easier access to information about CH online may have led to self-referral and self-diagnosis, this way improving patients' delay (41, 42, 51).

The rate of CH misdiagnosis was as high as 60-80% in several studies (14-16, 51), with an average number of incorrect diagnosis ranging from 2-3.9 (41, 56). It is unclear why patients with late onset CH were more rapidly diagnosed than those with early onset (17). This may be due to low prevalence and poor recognition among children (14, 17). It is possible that clinicians erroneously view CH as a disorder with onset predominantly in late adulthood. Another explanation might be that clinicians are more suspicious of a sinister cause for the

symptoms if the patient is older, and therefore have a lower threshold to refer to a neurologist although there are no studies that have assessed this. There is an increase recognition of CH amongst women, reflected by the reduction in the male:female ratio over the years (from 6:1 in 1992 (13) to 2:1 in 2017 (16)). Yet, a previous study established that the diagnostic process was more complex for women than men (16). Misdiagnosis was more frequent in women, and more women were not correctly diagnosed until seen in a specialised headache centre (16, 51). However, two studies showed equal diagnostic delay in men and women (42, 59).

2.5.2 Misdiagnosis and mismanagement

Misdiagnosis invariably leads to mismanagement. Due to the severity of the symptoms, patients with CH desperately seek the opinion of several specialists until the symptoms are alleviated. It is possible that some specialists feel the need to offer invasive procedures in an attempt to provide some form of relief, even if the chance of success is small. A high proportion of patients with CH undergo invasive procedures from dental surgeons and ENT specialists when a clear indication for such interventions was lacking (42). These results suggest that further awareness is required, particularly in the dental and ENT professions regarding the pain and cranial autonomic symptoms of CH mimicking dental and sinus pathologies, to avoid unnecessary and potentially harmful procedures.

In an attempt to treat their symptoms, patients with CH are more likely to employ extreme measures. The use of illicit drugs among CH sufferers is common (12, 41). They are also more inclined to have recourse to non-evidence based and non-pharmacological treatments (12, 14). This further supports the need for timely diagnosis and initiation of evidence-based treatments, and patient education. The evidence suggests that even after the correct diagnosis is reached, some patients received poor or incorrect information about the nature of their disability (15). Suboptimal management is not limited to the CH sufferers since most headache patients are undertreated, hence the importance of headache centres and promoting education of GPs (60). If a clinician has a suspicion of CH, this should trigger referral to specialised headaches centres for a correct diagnosis and initiation of appropriate treatment and to minimise the wastage of healthcare resources and unnecessary procedures.

2.5.3 Factors involved in diagnostic delays

A lack of knowledge of the characteristics of CH is likely to influence the clinician to seek an alternative diagnosis. Some CH characteristics could lead the clinician astray. For example, migraine features (e.g. aura, photophobia, phonophobia, nausea, vomiting) and a family history of migraine are often encountered in patients with CH (54). The presence of migraine-like features prolonged the delay to diagnosis as showed in several studies (51, 54, 59). Yet, other studies did not find a link between migraine-like features and diagnostic delays (14, 17, 61). Further research is required to establish the relationship between migraine-like features and delays in diagnosis. Attacks lasting longer than 180 minutes have been suggested as a cause of clinicians' delay, due to the confusion as to whether patients suffer from migraine (duration between four and 72 hours) (17, 56, 59).

The features of the CH pain may also mislead the clinician in making the wrong diagnosis. Although CH affects the first division of the trigeminal nerve while trigeminal neuralgia the second or third and exceptionally the first division, trigeminal neuralgia was the second most received misdiagnosis in two studies (15, 51). The presence of stereotyped attacks associated with cranial autonomic symptoms, the absence of triggers and the totally different duration and pain quality, still qualifies trigeminal neuralgia as one of the most received misdiagnosis (15, 41, 51). It is possible that clinicians are more aware of trigeminal neuralgia, even though CH is more common (incidence 53/100.000 (2) versus 4.5/100.000 (62)) but there no studies that validated this. The presence of side shift between attacks was also correlated with diagnostic delay possibly because CH is defined as 'unilateral pain' as per ICHD-3 criteria (1).

This review showed that the presence of episodic CH delayed the diagnosis, possibly due to long remissions and failure to seek medical help (14, 15, 54). A more recent Danish study failed to confirm these findings (59). This underlines the importance of further research to establish the role of clinical phenotype (episodic versus chronic CH) in diagnostic delays. Nocturnal attacks, a common feature of CH, although not present in the ICHD-3 criteria was found to delay the diagnosis (54, 59). As many as 77% of patients with CH have nocturnal attacks (4, 54, 59). This could influence patients' delay, meaning that patients wait longer before contacting their health professional, as long as daily work life remains unaffected (29). Restlessness during the attacks, a classical feature of CH can delay the diagnosis (1). The presence of restlessness prolonged the diagnosis in a Dutch study (54), although this was not confirmed in a Danish study (59).

2.5.4 Strengths and limitations

This is a rigorous systematic literature review on the delays in diagnosis and misdiagnosis of CH. A detailed search strategy of 10 electronic databases was used with no date or language restrictions. This systematic literature review included larger studies that could demonstrate rigorous analysis and studies with less than 10 patients and case reports were excluded.

The present study was subjected to limitations. Due to the paucity of studies in this area we did not exclude studies on the basis of quality appraisal. One limitation was the difficulty to compare the magnitude of the diagnostic delay between studies as different statistics were reported (mean, median or percentage). Certain variables established for data extraction were lacking in some studies. Statistical significance of the results was not performed in some studies. It is possible that the systematic literature review on the delays in diagnosis and misdiagnosis missed relevant studies despite a comprehensive search strategy across multiple databases with no date or language restrictions.

The literature search for this systematic literature review was conducted in May 2017. Therefore, this review needs updating. A search of Pubmed in May 2020 revealed three additional studies which are discussed below.

2.5.5 Summary of articles published between 2017 and 2020

A search of Pubmed on 26th May 2020 using the search terms 'cluster headache', 'diagnostic delay' and 'misdiagnosis' revealed three additional studies (59, 63, 64). One study was on cluster-like attacks due to adult-onset mitochondrial encephalopathy and considered irrelevant for this review (63). Two studies were relevant and are discussed further.

In his study on 400 patients with CH, Frederiksen et al. found a mean diagnostic delay of 6.3 years (range 0-47, median 3 years) (59). The diagnostic delay became significantly shorter with every decade from the 1950-2010 (59). CH patients with lower age of onset experienced significantly longer diagnostic delay than patients 20–40 years of age and patients > 40 years of age (59). Half of the patients (49%) were misdiagnosed before receiving a correct diagnosis of CH (59). The most common misdiagnosis was migraine (n=92, 23.5%), followed by TTH (n=76, 19.0%), and sinusitis (n=56, 14.0%) (59). Diagnostic delays affected men and women equally (59). On average, misdiagnosed patients had received 1.7 incorrect diagnoses. Clinical characteristics such as long attack duration, migraine-like features and nocturnal attacks were all associated with long diagnostic delay (59). The second study conducted by

Joshi et al., assessed the burden of CH on 75 patients (male:female ratio of 4:1) (64). The average time from first symptom onset to diagnosis was 12.7 years (range 1 to 51) (64). The average number of yearly emergency department and outpatient visits for the group of patients with CH was 4.5 and 25.4, respectively (64).

These two recent studies confirmed the delays in diagnosis and misdiagnosis of CH shown in the systematic literature review (36). Migraine remains the most received misdiagnosis among patients with CH, while TTH was reported as the second type of misdiagnosis in one of the studies (59). Although the systematic literature review revealed trigeminal neuralgia as the second most received misdiagnosis (15, 36, 41, 51), TTH was also among the reported misdiagnosis (16). Furthermore, this recent research strengthens the findings of the systematic literature review by which the presence of migraine like-features and long duration of attacks prolong the diagnosis of CH (36, 59). This leads to high healthcare cost due to multiple presentations to the emergency departments and numerous outpatient visits (64).

2.6 Conclusions

This is a robust literature review focused on the delays in diagnosis and misdiagnosis of CH. CH delays in diagnosis and misdiagnosis is not confined to a geographical area and is present in multiple countries around the globe. Both patients' and clinicians' factors account for the delays in diagnosis. Patients with CH occasionally waited before seeking medical advice and when they did, they visited many clinicians and received multiple misdiagnosis prior to being correctly diagnosed. The failure to diagnose patients with CH leads to poor management, disability and misuse of healthcare resources.

CHAPTER 3. PATHOPHYSIOLOGY OF CLUSTER HEADACHE: A LITERATURE REVIEW

3.1 Introduction

This chapter presents a literature review of the pathophysiology of CH, including neuroimaging, neuropeptide and genetic studies (37). Firstly, this chapter addresses the structural and functional studies which have provided insight into the network bases of CH. Secondly, the activation of the trigeminovascular system and the release of neuropeptides (calcitonin gene related peptide, neurokinin A, substance P, nitric oxide synthase, pituitary adenylate cyclase activating peptide, vasoactive intestinal peptide, neuropeptide Y, acetylcholine, noradrenaline, adenosine triphosphate) is discussed. The role of the hypothalamic neuropeptides (orexin-A and orexin-B) is also addressed. Finally, I present the role of different genes (hypocretin neuropeptide precursor gene, alcohol dehydrogenase 4 gene, circadian locomotor output cycles kaput gene, CACNA1A) in the pathophysiology and diagnosis of CH.

3.2 Methods

A review of the literature was carried out by searching PubMed and Web of Science. The search was conducted using the following keywords: imaging studies, voxel-based morphometry, diffusion-tensor imaging, diffusion magnetic resonance imaging, tractography, connectivity, cerebral networks, neuromodulation, central modulation, deep brain stimulation, orexin-A, orexin-B, tract-based spatial statistics, single-photon emission computer tomography studies, positron emission tomography, functional magnetic resonance imaging, magnetic resonance spectroscopy, trigeminovascular system, neuropeptides, calcitonin gene related peptide, neurokinin A, substance P, nitric oxide synthase, pituitary adenylate cyclase activating peptide, vasoactive intestinal peptide, neuropeptide Y, acetylcholine, noradrenaline, adenosine triphosphate, genetics, hypocretin neuropeptide precursor gene, alcohol dehydrogenase 4 gene, circadian locomotor output cycles kaput gene, CACNA1A. ‘Cluster headache’ was combined with each keyword for more relevant results (e.g. ‘cluster headache’ + ’imaging studies’, ‘cluster headache’ + ’neuropeptides’). All irrelevant and duplicated records were excluded

from consideration. Works published from October 1976 to September 2018 are presented in the current review.

3.3 Results

In this section, I first present the findings on neuroimaging studies in CH including structural, functional and biochemical studies. I continue with describing the anatomy of the trigeminovascular pain pathways relevant for CH pathophysiology. I also present relevant studies on the activation of the trigeminovascular pathway system and release of neuropeptides from the trigeminal, sympathetic and parasympathetic fibres. I conclude with a section on the genetic studies relevant for CH pathophysiology.

3.3.1 Neuroimaging studies

In this section, I present neuroimaging studies in CH including structural, functional and biochemical studies. I first discuss studies that investigated the brain structure of patients with CH using voxel-based morphometry (VBM), diffusion-tensor imaging (DTI) and tract-based spatial statistics (TBSS) and diffusion tractography. I continue with a section on functional imaging studies including single-photon emission computer tomography (SPECT) (65-67), positron emission tomography (PET) (68, 69) and functional magnetic resonance imaging (fMRI) studies. (70, 71). I conclude with a section on biochemical changes in CH investigated with magnetic resonance spectroscopy.

3.3.1.1 Structural studies

This section presents different imaging techniques such as VBM, DTI and diffusion tractography to investigate the brain structure of patients with CH.

Voxel based morphometry

Voxel-based morphometry (VBM) is a structural imaging technique that allows investigation of focal differences in brain anatomy and it is mainly used to identify grey matter alterations. VBM, used in a pioneering study by May et al. inspired many researchers to use the technique in the study of pain (72). It showed the involvement of the posterior hypothalamus in the pathophysiology of CH (72). This study conducted on 25 patients, detected significant structural differences (increase in volume) in gray matter density among patients with CH

compared to controls (72). A PET study on the same patient cohort showed activation of the same brain area (72). These findings led to the conclusion that the changes might be permanent and not a reaction to pain, showing a clear correlation between the structural and functional changes in CH (72). Matharu who reproduced the study found no alterations of the grey or white matter suggesting that the initial finding might be due methodological limitations (73). A more recent study, carried out by Absinta et al., showed alterations of brain structures involved in pain processing (reduced grey matter volume in the right posterior cingulate cortex, the head of the right caudate nucleus, right thalamus, left inferior parietal lobe, right middle temporal gyrus, left insula, right precentral gyrus, the bilateral frontal gyrus) (74). Using the same imaging technique, reduction of grey matter in frontal areas was detected in 49 patients with CH, findings interpreted as dysfunction of the descending pain modulation systems in CH (75). The same study detected grey matter increase in the anterior cingulate gyrus, insula and fusiform gyrus, changes that could represent compensation mechanisms or neuroplasticity (75). The largest VBM study in 2014 showed brain alterations (temporal lobe, hippocampus, insular cortex and cerebellum) related to the disease burden and variable in relation to the pain state (76).

Although multiple studies explored the role of posterior hypothalamus in CH, a recent study showed enlargement of the anterior hypothalamus in patients with both episodic and chronic CH compared with patients with migraine (77). Located in the anterior hypothalamus, the suprachiasmatic nucleus, which is the endogenous biological clock, might cause the circadian and circannual periodicity that characterizes CH (77).

Diffusion-tensor imaging / Tract-based spatial statistics /Tractography

Diffusion-tensor imaging (DTI) is an MRI technique used to estimate the axonal white matter organization of the brain. The data is collected by diffusion weighted images (DWI). The main parameters measured with DTI are fractional anisotropy and diffusivity (78, 79). Anisotropy is the property of being directionally dependent, which implies different properties in different directions, as opposed to isotropy (78). Fractional anisotropy is a scalar value from zero to one and describes the anisotropy of a diffusion process. Fractional anisotropy with a value of zero means the diffusion is isotropic (unrestricted or equally restricted in all directions). A value of one means that the diffusion affects one axis and it is restricted along the other axis (79, 80). The statistical analysis is performed using tract-based spatial statistics (TBSS) (81). TBSS uses image transformation that combines the strength of both voxelwise and tractography-based analyses (81).

The VBM study performed by Absinta et al. and described above, used a DTI/TBSS analysis on the same sample of patients but no significant change in fractional anisotropy or diffusivity was found (74). Another three studies that used DTI to explore the brain changes in CH, found widespread alterations in the pain processing system ('pain matrix') (80, 82, 83). Interictal alterations of the subcortical structures are present in CH (right amygdala, right caudate, right pallidum) (84). Some of the microstructural changes are related to lifetime disease burden, suggesting that recurring painful episodes might trigger maladaptive plasticity or degenerative processes (84).

Diffusion tractography is a 3D reconstruction technique to assess white matter pathways using the data collected by DTI (85). The tractography studies have shown that the deep brain stimulation (DBS) activated area lies in the ventral tegmental area, posterior to the hypothalamus (86-88) and projects to the ipsilateral cerebellum and thalamic reticular nucleus (88, 89).

Other structural imaging studies

Seifert et al. conducted a high resolution T1 weighted MRI study and performed whole-brain surface-based comparison of cortical thickness (90). The study showed cortical thickening in patients with CH, implying the involvement of the cortical structures in the pathogenesis of CH (90).

3.3.1.2 Functional studies

This section presents findings on relevant functional studies for the pathophysiology of CH. Different techniques were used in order to investigate the functional changes in CH including single-photon emission computerised tomography (SPECT), positron emission tomography (PET) and functional magnetic resonance (fMRI).

Single-photon emission computer tomography studies

Single-photon emission computerised tomography (SPECT) studies have been used as an early neuroimaging technique to evaluate the cerebral blood flow by 133-Xenon inhalation. The studies showed variable results - some reported increase (66, 91) others decrease (91) and some no changes in the cerebral blood flow (65, 67, 92). The last SPECT study showed reduced cerebral blood flow in the thalamus and posterior parietal areas contralateral to the pain side, hypothesizing early involvement of these brain areas in CH pathophysiology (93).

Positron emission tomography studies

Positron emission tomography (PET) is a nuclear medicine magnetic imaging technique that detects gamma rays emitted by positron-emitting radionuclide (tracer). The biological molecule chosen for PET is fludeoxyglucose, an analogue of glucose (94). The first nitroglycerin-induced PET study was conducted by Hsieh et al. in 1996 on seven patients with episodic CH and showed activation of brain areas involved in central nociception with preference to the right hemisphere (68). Although the initial PET study did not show activation of the hypothalamus, the study conducted by May et al. two years later showed activation of the inferior hypothalamic grey matter ipsilateral to the headache side during nitroglycerine-induced attacks (69). A later PET/MRA study by the same research group on a larger population of 17 patients with episodic CH showed activation of the inferior posterior hypothalamus and brain areas involved in pain processing (95). Significant dynamic changes in the brain metabolism during and outside CH attacks were detected by three PET studies carried out by Sprenger (96-98).

Functional magnetic resonance imaging studies

Functional magnetic resonance imaging (fMRI) measures brain activity by detecting changes associated with blood flow and relies on the fact that blood flow and the cerebral activation are coupled. When a brain area is active the blood flow to that area increases (99). The primary form of fMRI uses blood-oxygen-level-dependent contrast and measures changes in blood flow and tissue oxygenation (99). Resting-state fMRI is a technique that assesses the baseline brain activity when the subjects are not performing any task in contrast to task specific fMRI (100). In the first fMRI study, Morelli et al. showed activation of the hypothalamus during the CH attacks and activation of other brain areas involved in pain processing (70). The role of hypothalamus in the pathophysiology of CH was strengthened by several studies that found abnormal functional connectivity of the hypothalamus (71, 101-104). Involvement of the pain matrix as well as non-traditional pain processing areas (e.g. salience networks, occipital area, cerebellar network) were also found (100, 104). Metabolic normalization in the pain matrix areas and absent short-term changes induced by occipital nerve stimulation (ONS) might support the hypothesis that ONS, a symptomatic treatment for CH works through slow neuromodulation process (105).

3.3.1.3 Biochemical studies

31P-Magnetic resonance spectroscopy (31P-MRS) can be used as a non-invasive tool for measuring the relative intracellular concentrations of phosphorus containing metabolites in different organs (106). Montagna et al. conducted the first 31P-MRS study on 14 patients with CH and showed abnormalities in the brain energy metabolism with reduced phosphocreatine levels, increased adenosine diphosphate concentration, reduced phosphorylation potential and high relative rate of adenosine triphosphate biosynthesis (107). A few years later, Lodi et al. showed reduced cytosolic free Mg^{2+} and free energy released by the reaction of ATP hydrolysis (108). The first in vivo proton magnetic resonance spectroscopy (1H-MRS) studies to show the involvement of the hypothalamus in CH pathophysiology were performed in 2006 (109, 110). 1H-MRS allows non-invasive measurement of the signal intensities derived from N-acetylaspartate, creatine and phosphocreatine and choline-containing compounds (111). The studies showed reduced hypothalamic N-acetylaspartate-creatine ratio (109, 110) and reduced choline-creatine ratio (108) in patients with CH.

Table 3.1 presents a summary of the neuroimaging studies discussed in this section.

Table 3.1. Neuroimaging studies

Neuroimaging type	Author	Modality/Analysis method	No of subjects and diagnosis	Main findings
Structural studies				
	May et al. 1999 (72)	sMRI-T1w/VBM	25 ECH	Increase in bilateral posterior hypothalamic GM
	Matharu (Ph thesis) 2006 (73)	sMRI-T1w/VBM	66 ECH	No significant changes in GM and WM
	Owen et al. 2007 (88)	DW-MRI/ Probabilistic tractography	1 CCH	No CH attacks at 8 months after the DBS electrode was placed 6mm posterior to the hypothalamus, 2mm lateral and 8mm below the mid-commissural point
	Absinta et al. 2012 (74)	sMRI-T1w/VBM and TBSS	15 ECH	1.GM decrease in the pain network 2.GM increase in the right cuneus 3.No changes seen within the hypothalamus
	Teepker et al. 2012 (82)	sMRI-DTI/TBSS	7 ECH	Widespread WM alterations involved in trigeminal/nociceptive processing
	Seifert et al. 2012 (90)	sMRI-T1w/whole brain surface-based comparison of cortical thickness	12 ECH	Cortical thinning in the contralateral angular and precentral gyrus
	Yang et al. 2013 (75)	sMRI-T1w/VBM	49 ECH	1.GM volume reduction in frontal areas 2.GM increase in the ACC, fusiform gyrus, insula (longitudinal analysis)
	Szabo et al. 2013 (83)	sMRI-DTI/TBSS	13 ECH	Widespread reduction in FA and increase in diffusivity (contralateral dominance)
	Naegel et al. 2014 (112)	sMRI-T1w/VBM	68 ECH 23 CCH	GM volume alterations in the temporal lobe, hippocampus, insular cortex and cerebellum
	Chou et al. 2014 (80)	sMRI-DTI/TBSS	17 ECH	High diffusivities in the left frontal gyrus and lower diffusivities in the right parahippocampal gyrus
	Kiraly et al. 2017 (84)	sMRI-T1w and DTI/ FSL	22 ECH	1.Increased FA of the right amygdala 2.Increased diffusivity in the right caudate

			3.High radial diffusivity and lower anisotropy in the right pallidum
Arkink et al. 2017 (77)	sMRI-T1w/VBM	24 ECH 23 CCH 14 Probable CH	Increased volume of the anterior hypothalamus in patients with ECH and CCH; Similar trends but not significant in patients with probable CH
Akram et al. 2017 (86)	DW-MRI/VBM/ Probabilistic diffusion tractography	7 CCH	The DBS-activated area posterior to the hypothalamus in the ventral tegmental area lies on the tract that connects the hypothalamus, prefrontal, and temporal regions with brainstem area
Seijo et al. 2018 (87)	DW-MRI/ Probabilistic diffusion tractography	15 CCH	Projections between the DBS target areas and ipsilateral cerebellum and thalamic reticular nucleus
Functional studies			
Norris et al. 1976 (65)	SPECT/ROI	1 ECH	No changes in the mean CBF
Sakai et al. 1978 (66)	SPECT/ROI	8 ECH	Increased CBF
Henry et al. 1978 (67)	SPECT/ROI	3 ECH	No changes in the mean CBF
Nelson et al. 1980 (91)	SPECT/ROI	26 ECH	Variable changes in the mean CBF (increase or decrease)
Krabbe et al. 1984 (92)	SPECT/ROI	9 ECH 9 CCH	No changes in the mean CBF
Di Piero et al. 1997 (93)	SPECT/ROI	7 ECH	Decreased CBF in the posterior parietal cortex and thalamus contralateral to the pain side
Hsieh et al. 1996 (68)	PET/VBA and ROI	7 ECH	1.Decreased rCBF in the frontal cortex, posterior parietal cortex, occipito-temporal regions 2.Increased rCBF in the ACC, frontal cortex, insula, putamen, temporo-polar region with preference of the right hemisphere
May et al. 1998 (69)	PET/VBA	9 CCH	1.Exclusive activation during CH attacks of the inferior hypothalamic grey matter ipsilateral to the headache side 2.Increased rCBF in the ventroposterior thalamus, ACC and in the insula bilaterally
May et al. 1999 (72)	PET/VBM	17 ECH	Activation of inferior-posterior hypothalamus ipsilateral to the headache side

May et al. 2000 (95)	PET and MRA/VBA	17 ECH	1.Activation of the inferior posterior hypothalamus, frontal lobes, insula bilaterally, ACC bilaterally, ipsilateral thalamus, ipsilateral basal ganglia, contralateral inferior frontal cortex 2. Increased CBF in the ICA ipsilateral to the headache side
Sprenger et al. 2004 (96)	PET/VBA and ROI	1 CHH	1.Activation of the inferior hypothalamic grey matter 2.Increased rCRB in the medial thalamus and contralateral ACC
Sprenger et al. 2006 (97)	PET/VBA and ROI	6 ECH 1 CCH	Decreased tracer binding in the pineal gland
Sprenger et al. 2007 (98)	PET/VBA	11 ECH	1.Increased metabolism in the perigenual ACC, posterior cingulate cortex, prefrontal cortex, insula, thalamus and temporal cortex 2.Decreases in metabolism in the cerebellopontine area, perigenual ACC, prefrontal and orbitofrontal cortex
Morelli et al. 2009 (70)	fMRI/VBA	4 ECH	Activation of hypothalamus ipsilateral to the pain side, pre-frontal cortex, ACC, contralateral thalamus, ipsilateral basal ganglia, insula bilaterally and the cerebellar hemispheres
Rocca et al. 2010 (71)	fMRI/ICA and SB-FCA	13 ECH	1.Decreased fluctuations in the primary visual and sensorimotor networks 2.Increased FC in the hypothalamus and thalamus
Magis et al .2011 (105)	FDG-PET	10 CCH	Metabolic normalization in the pain matrix areas and absent short-term changes induced by ONS
Qiu et al. 2013 (101)	fMRI/SB-FCA	12 ECH	Abnormal FC of the hypothalamus located mainly in the pain system during the spontaneous CH attacks; It extends beyond the pain system during CH attack intervals.
Qiu et al. 2015 (102)	fMRI/ICA	21 ECH	1.Decreased functional coactivation between the hypothalamus, both ipsilateral and contralateral to the headache side, and SN in patients with right-sided or left-sided CH.
Yang et al. 2015 (103)	fMRI/SB-FCA	18 ECH	1.Hypothalamic FC changes with the medial frontal gyrus and occipital cuneus during and outside CH attacks 2.The annual bout frequency correlated with the hypothalamic FC in the cerebellar areas

Chou et al. 2017 (104)	fMRI/ICA	17 ECH	1.FC changes in the temporal, frontal, salience, default mode, somatosensory, dorsal attention and visual networks, independent of bout period 2.Altered FC in the frontal and dorsal attention networks during CH attacks
Farago et al. 2017 (113)	fMRI/ICA	17 ECH	Increased connectivity in attention network ipsilateral to the headache side and in the contralateral cerebellar network
Ferraro et al. 2018 (114)	RS-fMRI	17 CCH	1.Increased functional connectivity between the posterior hypothalamus and ventral tegmental area, dorsal nuclei of raphe, bilateral substantia nigra, sub-thalamic nucleus, red nucleus 2.No difference between patients and controls was found in the contralateral hypothalamic regions
Biochemical studies			
Montagna et al. 1997 (107)	31P-MRS/ROI	14 CH	Reduced phosphocreatine levels, increased ADP concentration, reduced phosphorylation potential, high relative rate of ATP biosynthesis
Lodi et al. 2001 (108)	31P- MRS/ROI	13 CH	Reduced cytosolic free Mg 2+ and free energy released by the reaction of ATP hydrolysis
Lodi et al. 2006 (109)	IH-MRS/ROI	18 ECH 8 CCH	Reduced hypothalamic N-acetylaspartate/creatine
Wang et al. 2006 (110)	IH-MRS/ROI	47 ECH	Reduced hypothalamic N-acetylaspartate/creatine and choline/ creatine

Abbreviations: ECH: episodic cluster headache; CCH: chronic cluster headache; GM: grey matter; WM: white matter; sMRI: structural magnetic resonance imaging; T1w: T1 weighted magnetic resonance imaging; RBF: cerebral blood flow; DTI: diffusion tensor imaging; FA: fractional anisotropy; VBM: voxel-based morphometry; TBSS: tract-based spatial statistics; ROI: region of interest; rCBF: regional cerebral blood flow; SPECT: single-photon emission computer tomography; VBA: voxel-based analysis; ACC: anterior cingulate cortex; ICA: internal carotid artery; PET: positron emission tomography; FDG-PET: fluorodeoxyglucose-positron emission tomography; ICA: independent component analysis; SB-FCA: seed-based functional connectivity analysis; FC: functional connectivity; SN: salience networks; IH-MRS: In vivo magnetic resonance spectroscopy; 31P-MRS: Phosphorus magnetic resonance spectroscopy; ATP: adenosine triphosphate; ADP: adenosine diphosphate; MRA: magnetic resonance angiography; DW-MRI: diffusion weighted- magnetic resonance imaging; DBS: deep brain stimulation; ONS: occipital nerve stimulation; RS-fMRI: resting state functional magnetic resonance imaging

3.3.2 The trigeminovascular pain pathways and neuropeptides

In this section, I first describe the anatomy of the trigeminovascular pathways relevant for the pathophysiology of CH. I continue with a section on the activation of the trigeminovascular system and release of neuropeptides. I conclude with a section on neuropeptide studies in CH, including peptides released from the trigeminal, sympathetic and parasympathetic nerve fibres.

3.3.2.1 Anatomy of the trigeminovascular pain pathways

The trigeminovascular system includes the trigeminal ganglion, the meningeal vasculature, distinct nuclei of the brainstem, thalamus and the somatosensory cortex (see Figure 3.1)(115). Pseudo-unipolar primary afferent fibres from the trigeminal ganglion synapse on intra- and extracranial structures (115). Nociceptive fibres innervating the pial, arachnoid and dural blood vessels including large cerebral arteries, superior sagittal sinus and middle meningeal artery arise from the trigeminal nerve, mostly V1 (116). On the other hand, the sensory fibres innervating the posterior fossa and basilar arteries are located in the C1-C3 dorsal root ganglia (117). The projections from the trigeminal ganglion and upper cervical nerve roots converge at trigeminocervical complex. The second-order neurons from trigeminocervical complex ascend in the trigeminothalamic tract and synapse with the third-order neurons (116). The third-order thalamocortical neurons synapse with a complex cortical network including the primary and secondary motor, sensory and visual areas (116). There are direct and indirect ascending projections to the hypothalamus, periaqueductal grey, locus coeruleus (118). There is a reflex connection from the trigeminal nucleus to the superior salivatory nucleus which projects via sphenopalatine ganglion (116). Additional ascending projections exist to the insula, retrosplenial, ectorhinal, rostral ventromedial medulla, parietal association and auditory areas (116). The thalamus is the relay centre involved in the modulation and processing of all incoming sensory information (119). The pain matrix that includes the thalamus, the primary and secondary somatosensory areas, the anterior cingulate gyrus and the prefrontal cortex are active during nociceptive processing (119). Furthermore, indirect projections from the trigeminal nucleus to the amygdala and hippocampus are likely to be involved in the processing of cognitive and affective responses to pain (120).

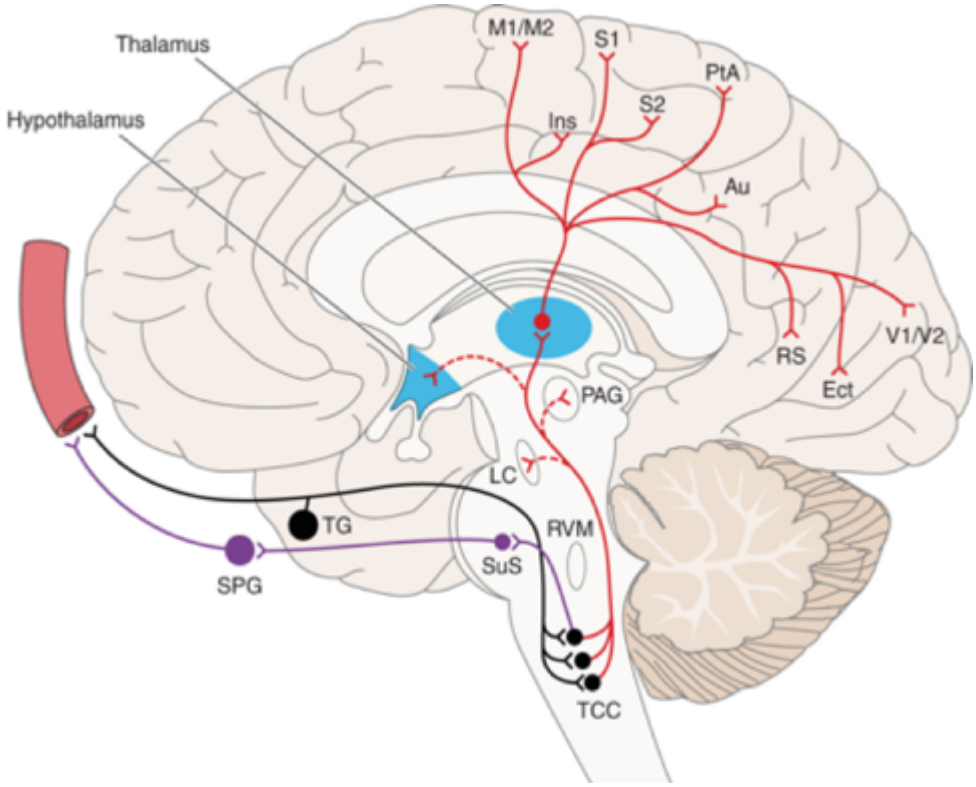


Figure 3.1. The ascending pathways of the trigeminovascular system (Reproduced from Goadsby et al. Pathophysiology of migraine: a disorder of sensory processing. Physiological reviews. 2017;97(2):553-622 with permissions from The American Physiological Society) (116)

Abbreviations: TCC: trigeminocervical complex; SusS: superior salivatory nucleus; LC: locus coeruleus; Ins: insula; RS: retrosplenial; Ect: ectorhinal; RVM: rostral ventromedial medulla; PtA: parietal association area; Au: auditory association area; TG: trigeminal ganglion; SPG: sphenopalatine ganglion; PAG: periaqueductal grey; M1/M2: primary and secondary motor area, S1/S2: primary and secondary sensory areas; V1/V2: primary and secondary visual areas;

3.3.2.2 Activation of the trigeminovascular system

In vivo, human studies have shown activation of the trigeminovascular system during acute CH attacks (121) with distribution of pain in the ophthalmic division of the trigeminal nerve (1). The parasympathetic activation as a component of CH attacks involves the activation of the trigeminal-autonomic reflex and it manifests clinically as lacrimation, nasal congestion and rhinorrhea (122). The activation of the parasympathetic fibers is mediated through the facial nerve (123). It has been shown that the sphenopalatine ganglion stimulation (SPG) can relieve the CH pain (124, 125). The sympathetic overactivity could be explained by the dilatation of

the carotid artery secondary to parasympathetic activation and subsequent compression on the periarterial plexus of sympathetic fibres (126).

The activation of the trigeminovascular system leads to neuropeptide release from the trigeminal nerve fibers. Nerve fibers are classified based on their neuropeptide content. The trigeminal sensory fibers contain calcitonin gene related peptide (CGRP), neurokinin A, substance P, nitric oxide synthase and pituitary adenylate cyclase activating peptide (PACAP). Parasympathetic nerve fibers are rich in vasoactive intestinal peptide (VIP), neuropeptide Y, acetylcholine, nitric oxide synthase, PACAP and sympathetic nerve fibers contain norepinephrine, adenosine triphosphate and neuropeptide Y (115, 116). The neuropeptides and their role are summarized in Table 3.2. Relevant neuropeptide studies are discussed in the next section.

Table 3.2. Craniovascular nerve fibres and their vasoactive neuropeptides (adapted from Goadsby et al. 2017) (116)

Type of nerve fibers	**Neuropeptide/ Neurotransmitter**	**Role of neuropeptide/neurotransmitter**
Trigeminal sensory nerve fibers	Calcitonin gene related peptide	Vasodilatation and plasma extravasation (127)
	Neurokinin A	Initiation of expression of cytokines (128)
	Substance P	Vasodilatation (129) and plasma extravasation (130) Initiation of expression of cytokines (130)
	Nitric oxide synthase	Regulates blood flow (vasodilatation) (131) Prevents platelet activation (131) Inhibits monocyte adhesion/leucocyte function (131)
	Pituitary adenylate cyclase-activating peptide	Vasodilatation (132)
Parasympathetic nerve fibers	Vasoactive intestinal peptide	Potent vasodilator (133) Proinflammatory/anti-inflammatory effects (133)
	Neuropeptide Y	Vasodilatation (134)
	Acetylcholine	Vasodilatation (135) Mast cell degranulation (135)
	Nitric oxide synthase	Vasodilatation (131)
	Pituitary adenylate cyclase-activating peptide	Vasodilatation (132)
Sympathetic nerve fibers	Norepinephrine	Potent vasoconstrictor (136)
	Adenosine triphosphate	Vasoconstriction (137)
	Neuropeptide Y	Vasoconstriction (134)

3.3.2.3 Neuropeptide studies

In this section, I summarise relevant studies on neuropeptides released following trigeminovascular system activation and I address their relevance in the pathophysiology of CH. I first discuss studies on neuropeptides released from the trigeminal sensory nerve fibres, followed by peptides released from the parasympathetic nerve fibres and I concluded with studies on peptides secreted by sympathetic nerve fibres.

3.3.2.3.1 Trigeminal sensory nerve fibres

Here, I present studies on neuropeptides released by trigeminal sensory nerve fibres including calcitonin gene related peptide, substance P, neurokinin A, nitric oxide synthase and pituitary adenylate cyclase activating peptide.

Calcitonin gene related peptide

Calcitonin gene related peptide (CGRP) is a potent vasodilator, mainly expressed in the central nervous system (127). It contains 37 amino acids and has two isoforms: α-CGRP (CGRP1), located in the central and peripheral nervous system and β-CGRP (CGRP2) distributed in the enteric nerve fibres (138). Although the role of CGRP has been extensively studied in migraine, several studies investigated the involvement of CGRP in the pathophysiology of CH (121, 139, 140). Patients with spontaneous or nitroglycerine-induced CH attacks were found to have increased CGRP levels in the external jugular vein that were normalized after oxygen inhalation or treatment with subcutaneous sumatriptan 6 mg (121, 139, 140). These findings led to the development of a novel class of drugs, the monoclonal antibodies targeting the CGRP receptor or its ligand (29-31). The CGRP monoclonal antibody galcanezumab (Emgality®, Eli Lilly, Indianapolis, IN, USA) was reported effective and well tolerated in a placebo-controlled trial with one hundred and six patients with episodic CH (49 received galcanezumab and 57 received placebo) (29). Although the CGRP monoclonal antibodies have shown to be effective in one study with episodic CH patients, none of the studies have shown efficacy in chronic CH (29). A clinical trial of fremanezumab (Ajovy®, Teva, Petah Tikva, Israel) in both chronic and episodic CH failed to meet the endpoints of mean change from baseline in the weekly average number of CH attacks during a four-week treatment period and was stopped at the early stage (30, 31). In contrast, four CGRP monoclonal antibodies including erenumab (141), fremanezumab (142), galcanezumab (143, 144) and eptinezumab proved safe and effective in

patients with both episodic and chronic migraine (145, 146). It is unclear why the CGRP monoclonal antibodies are more effective in migraine patients compared to CH sufferers. Different levels of CGRP at baseline might have influenced the response to these class of drugs, although the current research has not explored this.

Substance P

Substance P is the first responder to most noxious stimuli and it is regarded as an immediate defence, stress, repair and survival system (147). Its receptor, neurokinin type 1, is distributed in many tissues and organs (147). Substance P is responsible for multiple functions. It is a potent vasodilator (129), has role in inflammation initiating the expression of cytokines (130) and it is involved in nociception and regulation of mood disorders (148). Substance P activity can be measured indirectly by assessing the somatostatin activity, effective in relieving CH attacks, which inhibits substance P release from the central and peripheral nervous system (149). Changes in substance P-immunoreactivity have been shown during spontaneous and histamine induced CH attacks suggesting a possible involvement of substance P in CH pathophysiology (149). Trigeminovascular system activation in cats induces release of substance P in the extracerebral circulation (150). Decreased substance P after administration of hyperbaric oxygen was found in patients with CH compared to controls (151).

Neurokinin A

Neurokinin A (formally known as Substance K) has an important contribution to nociceptive processing and inflammatory response, initiating the release of cytokines (128). Neurokinin A, together with CGRP and Substance P are released from the caudal trigeminal nucleus of the rat during electrical stimulation of the trigeminal ganglion (152). The main role of neurokinin A is vasodilatation. The order of potency is CGRP > Substance P > Neurokinin A (121).

Pituitary adenylate cyclase-activating peptide

Pituitary adenylate cyclase-activating peptide (PACAP) is involved in the regulation of important biological functions and is located in the brain and peripheral organs, notably the endocrine pancreas, gonads, respiratory and urogenital tracts (153). PACAP is found in both trigeminal sensory and parasympathetic fibres and its main role is vasodilatation (132). Although the role of PACAP was extensively studied in migraine (154-156), it was shown that PACAP-38 is released during CH attacks with significantly low levels during the inter-bout period (157). These findings support the role of PACAP-38 in the pathophysiology of CH.

Nitric oxide synthase

Nitric oxide synthases are a family of enzymes catalyzing the production of nitric oxide from L-arginin (158). Nitric oxide is a signaling molecule found in most tissues of the body. Among many other roles, nitric oxide controls neurotransmission and vascular tone (158). Nitric oxide production is correlated with disease activity of inflammatory disorders such as multiple sclerosis (159), systemic lupus erythematosus (160) and bacterial meningitis (161). Nitric oxide synthase regulates blood flow (vasodilatation), prevents platelet activation and inhibits monocyte adhesion and leucocyte function (131). Nitrates, which are reduced to nitric oxide in the body, are well known headache triggers (158). Enhanced nitric levels were found in the plasma (162) and cerebrospinal fluid (158) of patients with CH during the active and remission periods. Despite these findings, it has been shown that genetic variations within the nitric oxide synthase gene are less likely to contribute to CH susceptibility (163).

3.3.2.3.2 Parasympathetic nerve fibres

In this section, I summarise relevant studies on three main peptides released by the parasympathetic nerve fibres: vasoactive intestinal peptide, neuropeptide Y and acetylcholine.

Vasoactive intestinal peptide

Vasoactive intestinal peptide (VIP) is a peptide hormone of 28 amino acid residues that belongs to a glucagon/secretin family. VIP is a potent vasodilator and has proinflammatory and anti-inflammatory effects (133). VIP is found in the parasympathetic nervous system and suprachiasmatic nucleus, as well as the digestive and cardiovascular system (164). Elevated VIP plasma levels were found during CH as well as migraine attacks, suggestive of intense parasympathetic activation (150). Serum VIP, but not CGRP levels seem to reflect the rate of activation of the parasympathetic arm of the trigeminovascular system in migraine (165) but there are no studies that have tested the same in patients with CH.

Neuropeptide Y

Neuropeptide Y is a 36 amino-acid neuropeptide and the most abundant peptide in the central and peripheral nervous system. Neuropeptide Y is found in a high number of neurons of parasympathetic ganglia but it is produced mainly by the sympathetic nervous system. In the human brain, neuropeptide Y expression is highly concentrated in hypothalamic nuclei, basal ganglia, and limbic system (166). Neuropeptide Y can modulate nociceptive trigeminovascular

transmission in second-order neurons after peripheral systemic administration (167). Its main role is vasoconstriction although it can also have vasorelaxant effect (134). The earlier experiments from 1988 did not find changes of neuropeptide Y levels in the external jugular vein during attacks of CH (150). This may suggest a more localized locus of release, for example the hypothalamic nuclei, would not detect neuropeptide Y in the extracranial vessels.

Acetylcholine

Acetylcholine is the neurotransmitter used at the neuromuscular junction and it is released by the motor neurons to activate muscles. Acetylcholine is also used as a neurotransmitter in the autonomic nervous system, both as the final product released by the parasympathetic nervous system and as internal transmitter for the sympathetic nervous system (168). Parasympathetic fibres originating from the sphenopalatine ganglion and trigeminal nerves, release acetylcholine, VIP, and PACAP provoking mast cell degranulation and additional release of neurotransmitters, or they can directly affect trigeminal nerves inducing nociception (135). It is well known that parasympathetic activation is present in CH and other primary headaches (169). The acute electrical stimulation of the sphenopalatine ganglion provides significant pain relief and clinically meaningful reduction in CH attack frequency in some patients (34).

3.3.2.3.3 Sympathetic nerve fibres

Here, I present studies on two main neuropeptides secreted by the sympathetic nerve fibres including norepinephrine and adenosine triphosphate.

Norepinephrine

Norepinephrine, also called noradrenaline, is a potent vasoconstrictor. It is both a hormone and a neurotransmitter, produced by locus coeruleus in the pons and also released into the bloodstream by the adrenal glands (136). Tyrosine, tryptamine and tyramine, all involved in norepinephrine production, were found to be abnormal in patients with chronic CH (170, 171). These findings could suggest that anomalies in the tyrosine metabolism plays a role in the pathogenesis of CH (170, 171). A primary autonomic dysfunction in CH was also suggested by increased beta-receptor response to norepinephrine in patients with CH compared to controls (172).

Adenosine triphosphate

Adenosine triphosphate is a complex chemical compound involved in intracellular energy transfer. Adenosine triphosphate has several roles as excitatory co-transmitter in the peripheral nerves (137). It is co-stored with noradrenaline in the synaptic vesicles in postganglionic sympathetic fibers and has vasoconstriction properties (137). The existing magnetic spectroscopy studies have shown abnormal energy metabolism in patients with CH (107, 108).

3.3.3 Genetic aspects of CH

CH is believed to be a genetically susceptible disease, autosomal dominant genes playing an important role in some families (173). Positive family history occurs in 6.2 % of CH patients (173) and, compared to the general population, the risk of direct lineal descendants having CH is increased by 14-39 times (174-177). Here, I discuss the role of four main genes in CH including hypocretin neuropeptide precursor gene, alcohol dehydrogenase 4 gene, circadian locomotor output cycles kaput gene and *CACNA1A* gene.

3.3.3.1 Hypocretin neuropeptide precursor gene

Hypocretin, also known as orexin, is produced in the lateral and posterior hypothalamus. HCRTR1 and HCRT2 are hypocretin receptors. Hypocretin neuropeptide precursor gene encodes a neuropeptide precursor protein that gives rise to orexin-A and orexin-B and it is involved in a wide range of physiological processes, including pain transmission, neuroendocrine and autonomic function (178). Orexins play a major role in wakefulness and sleep pattern (179). Deficient orexin transmission is found in people with narcolepsy, characterised by excessive daytime somnolence, disturbed nocturnal sleep, hypnagogic hallucinations, sleep paralysis, and cataplexy (180). The orexins have been linked with a possible role in CH. The connection between CH and sleep has long been established (181). CH attacks are common at the onset of rapid eye movement (REM) sleep when the orexinergic system is down regulated to aid sleep onset (182).

A meta-analysis that included 593 patients with CH and 599 controls from three European studies have showed that the 1246G-A polymorphism (rs2653349) in the *HCRTR2* gene may modulate the risk of CH (183-186). In contrast, the largest population-based study conducted by Weller et al. in 2015 on 575 patients with CH and 874 controls found no evidence for association of rs2653349 and CH, but positive association was found in the

meta-analysis conducted by the same authors on six previously published studies (187). The meta-analysis results should be interpreted with caution, as individual population studies have limited power, therefore they have limited validity (187). A study on Chinese patients conducted by Fan et al. (112 patients with CH and 192 controls) did not find significant association between the hypocretin gene polymorphism and CH (188). Giving the inconsistency of the results from the reported studies, the exact role of *HCRTR2* gene in CH is yet to be established.

3.3.3.2 Alcohol dehydrogenase 4 gene

Alcohol is a well-known trigger factor for CH attacks during the active period (189). Alcohol is metabolized by alcohol dehydrogenase, a group of enzymes mainly present in the liver and gastrointestinal tract. Alcohol dehydrogenase 4 is encoded by the alcohol dehydrogenase 4 gene. Two studies conducted by Rainero at al. (110 patients with CH, 203 controls) and Zarrilli et al. (54 patients with CH, 200 controls) have shown significant correlation of the alcohol dehydrogenase 4 gene polymorphism and CH (190, 191). A large Swedish study (390 patients with CH, 389 controls) (192) and a Chinese study (112 patients with CH and 192 controls) have not confirmed the results (188). The reported studies have shown contradictory findings. It is possible that population differences might have led to varying results. Furthermore, the positive studies included a small number of patients and have limited validity.

3.3.3.3 Circadian locomotor output cycles kaput gene

CH is a disorder of the circadian rhythm. An abnormal internal circadian locomotor output cycles kaput (CLOCK) function of the hypothalamus is hypothesized to be involved in CH pathophysiology (193). Several studies investigated the association of the polymorphism of the human *CLOCK* gene (rs1801260) with CH (188, 191, 194, 195). However, no consistent evidence for association of *CLOCK* with CH was observed until recently when Fourier et al. found a significant association of *CLOCK* gene rs12649507 with CH (196). The large Swedish study that included 449 patients with CH and 677 controls, strengthened the hypothesis of the involvement of circadian rhythm in CH (196).

3.3.3.4 CACNA1A gene

Mutations of the P/Q type calcium channel alpha 1 subunit (CACNA1A) gene on chromosome 19p13 have been shown to cause a wide spectrum of disorders, mainly episodic diseases (197).

A missense mutation of the *CACNA1A* gene causes familial hemiplegic migraine (197). Although it was initially thought to be a potential gene for CH, it has been shown that the association between *CACNA1A* gene in sporadic CH is unlikely (197).

3.4 Discussion

In this section, I discuss the main findings from neuroimaging, neuropeptide and genetic studies. I first address the role of neuroimaging studies in the pathophysiology of CH. I continue with neuropeptide studies which gave insight into possible biological markers of CH. I will further discuss the role of the trigeminovascular system with subsequent release of neuropeptides. Genetic association studies and their current role in the diagnosis of CH are also discussed below.

3.4.1 The role of neuroimaging studies in CH

Studies conducted by Kudrow et al. were the first to implicate the hypothalamus in the pathogenesis of CH with the demonstration of lower levels of testosterone during a bout (198). Additional studies showed disordered circadian rhythm for cortisol, luteinizing hormone, growth hormone, and prolactin (199) and a suppressed nocturnal peak in melatonin is seen during the active phase of CH (200). Several neuroimaging studies have identified differences between patients with CH and control subjects in respect to brain structure. Neuroimaging studies have shown a clear correlation between the structural and functional changes in CH (201). The hypothalamus, an important component of the central nervous system, that plays a role in homeostasis, autonomic, endocrine function and nociception (202), has been hypothesized to play an essential role in initiating CH attacks. The neuroimaging findings led to the use of stereotactic stimulation of the activated brain areas identified by structural and functional imaging. Hypothalamic deep brain stimulation (DBS) was used successfully in treating refractory chronic CH (203). The latency of improvement or inefficacy of the hypothalamic DBS in the acute phase, might suggest that the hypothalamus has a modulating role of dysfunctional brain networks (203). Other reports suggest that the hypothalamus terminates rather than triggers the attacks (204). Although previous reports refer to the posterior hypothalamus as the optimal target, tractography studies have shown that DBS activated area it is not located within the anatomically-defined limits of the hypothalamus (86, 205, 206). The precise anatomical location for DBS refers to the midbrain tegmentum rather than the posterior

hypothalamus (89, 206). The neurons in the ventral tegmental area project to multiple brain regions and are involved in pain modulation, cognition, motivation and behavioral disorders (207).

Neuroimaging studies also implicate other brain areas generally associated with the pain matrix such as various brainstem areas, diencephalic structures, prefrontal cortex, basal ganglia, and parts of the limbic system (202). The pain matrix integrates all the sensory, affective and cognitive responses to pain and becomes active during nociceptive processing (116). These areas are involved in a broad range of chronic painful diseases and are not specific for headache disorders (208). The abnormal functional hypothalamic connectivity is well beyond the pain matrix (203), involving the default mode network (i.e. precuneus), middle frontal gyrus, cerebellum and visual areas (i.e. cuneus) (103). Furthermore, the central processing of the parasympathetic activity occurs in the areas of the default mode network (209). Hence, the typical cranial autonomic symptoms of CH explain the dysfunctional connectivity in regions belonging to the default mode network (209). More insight into the role of brain areas not traditionally involved in pain modulation (i.e. default mode network, occipital and cerebellar areas) is required. Abnormal metabolism in the perigenual anterior cingulate, prefrontal and orbitofrontal cortex suggests the involvement in the descending antinociceptive processing in patients with CH (98). It has been previously hypothesised that a deficient top-down modulation of antinociceptive circuits in CH patients promotes the initiation of the bout period and acute attack (98). It is recognized that alterations in the central and descending opioid system contributes to the chronification of pain (210). The microstructural changes present in patients with CH are related to lifetime disease burden, suggesting that recurring painful episodes might trigger maladaptive responses (84). Different sites such as the ventral tegmental area, the occipital nerve, the sphenopalatine nerve and the vagus nerve have been recognized as relevant pain pathways in the pathophysiology of CH. Neurostimulation of these pain pathways can influence central neurotransmitters (211).

The activation of the hypothalamus on functional neuroimaging studies is not specific for CH. Hypothalamic activation was reported in other TACs including SUNCT, SUNA and hemicrania continua (212-214) and also in migraine (215). Hypothalamic involvement during migraine attacks is more anterior than those reported in CH (116). Anterior hypothalamus, midbrain ventral tegmental area and periaqueductal grey are activated during the prodromal phase of migraine (216). In interictal migraineurs, changes in resting state functional connectivity of the dorsal pons was reported (217). The pontine network is specifically

involved in migraine attack generation and it is not present in CH (218). Future work should focus on the key differences between the pathophysiology of CH, other TACs and migraine.

3.4.2 The role of neuropeptides and genetic studies in CH

The release of neuropeptides as a consequence of trigeminovascular system activation was proposed as pain mechanism in CH and other primary headaches (219). The release of these peptides leads to a series of tissue responses including arteriolar vasodilation, plasma protein extravasation, and degranulation of mast cells in their peripheral target tissue (220). Among sensory neuropeptides, peripheral CGRP levels (121, 139, 140), VIP (165) and PACAP-38 (157) are reported to be good biomarkers of acute CH attacks. Nevertheless, these neuropeptides are not specific for CH as increased levels of CGRP (221), VIP (222) and PACAP were also found migraineurs (156). Serum VIP, but not CGRP, levels, seem to reflect the rate of activation of the parasympathetic arm of the trigeminovascular system in migraine but there are no studies that have tested the same in patients with CH (165). Several other neuropeptides are involved in the trigeminovascular system activation (substance P, neurokinin A, nitric oxide synthase, neuropeptide Y, acetylcholine, norepinephrine, adenosine triphosphate) but the existing evidence does not qualify them as reliable biomarkers in CH. Although there is a real need of biomarkers in CH, the current data must be interpreted with caution. The elevated levels of neuropeptides during the CH attacks could only suggest the activation of the trigeminovascular system, also present in other primary headaches.

The hypothalamic orexin-A and orexin-B have been linked with CH. Inconsistent results were found for the role of *HCRTR2* gene in the pathophysiology of CH. Genetic association studies in CH have shown discordant results. The strongest evidence was found between the association of *CLOCK* gene and CH, reinforcing the possible involvement of the circadian rhythm in CH (196). A genome wide association study will inform on possible diagnostic genetic markers of CH.

3.4.3 Strengths and limitations

This is a comprehensive literature review on the pathophysiology of CH, including neuroimaging, neuropeptide and genetic studies. Different imaging modalities were covered in this review (structural, functional, biochemical). Neuropeptides released by the trigeminovascular system as well as hypothalamic peptides are discussed. Genetic association studies are also addressed in this review.

Despite a detailed literature search, relevant articles might have been missed. There is need for a systematic literature review on the pathophysiology of CH and possible biological markers.

3.5 Conclusions

Neuroimaging and neuropeptide studies have revolutionized the understanding of CH pathophysiology. The neuroimaging studies revealed three major findings: activation of the posterior hypothalamic area during CH attacks, involvement of the pain matrix and involvement of the central opioid system. It is debatable whether the activation seen in these studies is the midbrain tegmentum or the posterior hypothalamus. Among neuropeptides, CGRP, VIP and PACAP-38 are increased during CH attacks. They are not specific for CH and can only suggest activation of the trigeminovascular system. Several other neuropeptides are involved in the trigeminovascular activation but the current evidence does not qualify them as reliable biomarkers in CH. The genetic studies show the strongest evidence in association with CH for the *CLOCK* gene. Although there has been important progress in understanding the pathophysiology of CH, a specific biomarker is yet to be found.

CHAPTER 4. DEVELOPMENT AND EVALUATION OF A SCREENING TOOL FOR THE DETECTION OF CLUSTER HEADACHE – A PROSPECTIVE OBSERVATIONAL STUDY

4.1 Introduction

This chapter first presents a background to CH diagnosis, including challenges with the detection of CH, key differences between CH and migraine, and previous screening tools for the detection of CH. The chapter continues with the development and evaluation of a 12-item screening tool for the detection of CH. The study consists of a three-step procedure. The first phase of the study consists in the development of the screening tool. The screening tool is comprised of three main components: six images depicting headache pain, verbal descriptors of pain and key questions that could differentiate between CH and migraine. In the second phase, the preliminary version of the tool was piloted on patients with CH and migraine and refined based on their feedback. In the third phase, the updated screening tool was further tested in a larger-scale study. The data analysis focused on the performance of the screening tool as a whole. The analysis also included the performance of individual test items and association between them.

4.2 Background to CH diagnosis

Here, I first present a section on the challenges with CH diagnosis including difficulties faced in primary care. Secondly, I continue with a section on key differences between the clinical characteristics of CH and migraine, the most common misdiagnosis. Thirdly, I present a section on previous questionnaires developed for CH diagnosis and I conclude with a section on visual tools used for pain assessment.

4.2.1 Challenges with the detection of CH

In the absence of clinically useful biological markers (36), CH is diagnosed based on history taking in accordance with the ICHD-3 criteria which is the gold standard (1). CH patients incur a high healthcare cost, estimated in the USA as greater than $2.8 billion/year (223). Although

CH has very distinct features, patients often face delay in diagnosis, misdiagnosis and mismanagement (14, 15, 41, 224). According to data from the systematic literature review, the most common misdiagnosis of CH is migraine (14-16, 51, 57). Patients with CH are first seen by multiple specialists including dentists, ENT specialists, opticians, ophthalmologists, psychiatrists, or pain specialists (42). Despite the substantial disability, patients with CH suffer many years with intense pain before the final diagnosis is made. Although the diagnostic delays of CH have decreased over the past decades (42), the interval between the onset of the disease and first consultation at a headache centre is still high (41). Patients with CH have difficulties at work and often require sick leave (225). Misdiagnosis of CH has a significant impact on patients' daily life, employment and mental health (53). It is important that CH is diagnosed early as effective therapies exist and should be recommended (28). A correct and timely diagnosis improves the quality of life, avoids unnecessary consultations and reduces the burden on the healthcare system (36).

Within the NHS, GPs act as front-line health professionals, differentiating patients that are treated in primary care from those who need specialist input (226). Although the GP gatekeeping was associated with lower healthcare use and cost, and better quality of care (227) it can have an important drawback: it may hamper timely diagnosis and treatment of patients suffering from uncommon diseases (228). This could result in referral delay, reduced quality of life and unnecessary healthcare cost (228). The GP gatekeeping system could be detrimental to patients with CH when the condition is not recognised. The early detection of CH could facilitate timely diagnosis and improve treatment pathways and CH management. The screening of CH can reduce the misuse of medical resources and unnecessary referrals to other specialities. Early detection strategies are used in primary care for conditions such as chronic obstructive pulmonary disease (COPD) (229), prostate cancer (230) and multiple myeloma (231). Screening questionnaires are occasionally used when biological markers are not available (232-234). Self-administered questionnaires have been developed for GPs to detect major depression (232), alcohol liver disease (233) and medication misuse (234). Self-administered questionnaires for the early detection of CH could be a quick and useful procedure in primary care.

4.2.2 Key differences between CH and migraine

This section emphasises the key differences between CH and migraine. I further discuss their clinical features and management.

4.2.2.1 Clinical characteristics

There are multiple features that differentiate CH from migraine. First, the severity and location of pain. The CH pain is strictly unilateral whereas in migraine could be bilateral (1). Bilateral CH attacks have been reported but exceptionally (235). The CH pain is excruciating and often described as a 'hot poker in the eye' (236). Because of the severity of pain, patients with CH exhibit restlessness behaviour or self-harm (5). In contrast, patients with migraine avoid physical activity during attacks (1). Secondly, the duration of pain differs. The cluster attacks last from 15 min to three hours whereas migraine attacks last from four hours to 72 hours when untreated (1). Cluster attacks are characterized by sudden onset and cessation. Although other primary headache disorders have associated cranial autonomic features, the intensity and frequency are more prominent in CH (169). Thirdly, a cluster attack is accompanied by at least one autonomic feature ipsilateral to the pain side including ptosis, miosis, eyelid oedema, conjunctival injection, lacrimation, nasal blockage, rhinorrhoea, facial or forehead sweating (1). The cranial autonomic features could be present in 56% of patients with migraine but are less severe, bilateral and inconsistently present from one attack to the other (169). An association with a personal history of smoking has been described for CH but not for other primary headaches (8, 237). Alcohol and sleep can trigger CH attacks (238) whereas migraine can have multiple triggers (239). Table 4.1 shows the differences in the clinical features of CH versus migraine.

Table 4.1 Clinical features of CH versus migraine

Clinical feature	CH	Migraine
Distribution of pain	Orbital, supraorbital and/or temporal pain (1)	Usually frontotemporal but can affect any part of the cranium (1)
Untreated attack duration	15 min-3 hours (1)	4-72 hours (1)
Severity of pain	Severe or very severe (1)	Moderate or severe (1)
Strict unilaterality of pain	Yes (1)	No (1)
Restlessness	Yes (1)	No (1)
Cranial autonomic features	94% of patients Severe, unilateral, consistently present from one attack to other (169)	56% of patients Less severe, bilateral, and inconsistently present from one attack to another (169)
Male:female ratio	2-3/1 (240)	1/3 (240)
Temporal pattern	Episodic CH: Frequent attacks (typically ≥1 daily), recurring in bouts (usually once or sometimes twice a year), which are typically of 6–12 weeks duration, then remitting for ≥3 months (240) Chronic CH: Similar, but without such remissions between bouts (240)	Episodic migraine: Frequency often 1–2/month but variable from 1/year to 2/week or more (240) Chronic migraine: Episodicity lost: headache on ≥15 days/month, having migrainous features on ≥8 days/month (240)
Circadian and circannual periodicity	Yes (193)	No (241)
Aggravation by routine physical activity	No (1)	Yes (1)
Association with smoking	Yes (242)	No (243)
Triggers	Alcohol (238), sleep (238)	Alcohol (238), sleep deprivation (116), weather changes (239), menstrual cycle (239)

4.2.2.2 Management

The management of CH and migraine consists of key differences but also similarities. The management of both conditions includes abortive therapy and preventative medication (28). Due to sudden onset of cluster attacks the abortive medication includes parenteral and intranasal administration. Sumatriptan (selective agonist of 5-hydroxytryptamine) 6 mg subcutaneous injection (the only triptan available for parenteral use) has rapid effect and high response rate (244). Placebo-controlled studies showed the efficacy of Sumatriptan (20mg) (18) and Zolmitriptan (5mg) by nasal spray in treating CH attacks (19). Due to long duration of migraine attacks, the abortive medication consists of oral administration of triptans (116). Inhalation of oxygen delivered through non-rebreathing masks relieves the pain within 15-20 minutes in the majority of CH sufferers (20) but oxygen is not an effective treatment for migraine (245). While non-steroidal anti-inflammatory medication are not effective in aborting CH attacks (8), they are often prescribed for migraine management (246). Furthermore, other key difference in the management of CH and migraine is represented by the long-term preventative treatment. CH's prophylaxis includes verapamil (26) and lithium (27) as first and second line choices while migraine is managed with amitriptyline, propranolol, topiramate (247), candesartan (248) or venlafaxine (249). Invasive neuromodulation techniques are treatment options for both refractory cases of CH and migraine. Although the occipital nerve stimulation is recommended for both conditions (250-253), the sphenopalatine ganglion stimulation (34) and hypothalamic deep brain stimulation (35) are reserved solely for patients with CH. However, non-invasive vagus nerve stimulation is recommended for both CH (32, 33) and migraine (254). The novel monoclonal antibodies against CGRP have been tested in both patients with CH and migraine. While galcanezumab proved to have moderate effect in episodic CH (29), fremanezumab failed to show effectiveness in both episodic and chronic CH (30, 31). Four CGRP monoclonal antibodies including erenumab (141), fremanezumab (142), galcanezumab (143, 144) and eptinezumab proved effective and safe in both episodic and chronic migraine (145, 146). Table 4.2 shows the management of CH versus migraine.

Table 4.2. Management of CH versus migraine

Management	CH	Migraine
Acute therapy	Oxygen (20) Sumatriptan subcutaneous injection (244) Sumatriptan nasal spray (18) Zolmitriptan nasal spray (28)	Sumatriptan oral (116) Non-steroidal anti-inflammatory medication (246)
Interim therapy	Greater occipital nerve block (28) Oral steroids (22-24)	Greater occipital nerve block (255)
Preventative therapy	Verapamil (26) Lithium (27) Topiramate (27) Melatonin (28)	Amitriptyline (256) Propranolol (247) Topiramate (256) Candesartan (248) Venlafaxine (249)
Novel prophylactic therapies (CGRP monoclonal antibodies)	Galcanezumab (29)	Erenumab (141) Galcanezumab (143, 144) Fremanezumab (142) Eptinezumab (145, 146)
Neuromodulation	Sphenopalatine ganglion stimulation (34) Occipital nerve stimulation (250-252) Hypothalamic deep brain stimulation (35) Non-invasive vagus nerve stimulation (32, 33)	Occipital nerve stimulation (253) Non-invasive vagus nerve stimulation (254)

4.2.3 Assessing existing screening tools for CH

Several research groups developed self-administered questionnaires for the detection of CH in tertiary headache centres (257, 258), general population (259-261) or web based (262). These studies' advantages and limitations are summarized in Table 4.3 and discussed further.

Research conducted by Dousset et al. showed that a three-item self-administered questionnaire had a high performance in detecting CH (sensitivity 78%; specificity 100%) (258). The study included a small sample size (37 patients with CH; 59 patients with migraine) and should be reproduced on a larger scale (258). Similarly, a self-administered questionnaire

with 16 items was tested by Torelli et al. in a tertiary headache centre on 71 patients (30 patients with CH, 21 patients with migraine, 30 patients with TTH) (257). The test items with the best performance included short duration of attacks (sensitivity 100%; specificity 90%) and the presence of restlessness during headaches (sensitivity 90%; specificity 92.%) (257).

A German research group led by Fritsche tested a 20-item questionnaire to diagnose migraine, TTH and TACs in a tertiary headache centre (259). This study included 278 patients, of whom 98 were diagnosed as TACs by physicians and 62 by questionnaire (259). However, the exact types of TACs are not specified, therefore the number of CH cases diagnosed is unknown (259). This questionnaire was further assessed in a general population with headache by Yoon et al. (260) and Kukava et al. (261). The questionnaire included specific questions regarding migraine (seven items), TTH (seven items) and TACs (six items) (259). An analysis algorythm based on the ICHD criteria was used to diagnose different types of headaches but the algorythm details were not provided (259). The questionnaire proved to be more useful at detecting migraine and TTH and it overdiagnosed patients with CH. Physicians confirmed only two cases of CH compared to 45 (260) and 16 (261) respectively diagnosed by the questionnaire. In a study from 2019, Chung et al. tested an eight-item questionnaire on a large cohort of patients (42 CH, 207 migraine, 77 TTH, 18 primary stabbing headache) (263). This study included only one patient with chronic CH, therefore the tool might not apply to the chronic forms of CH (263).

Previous research also assessed the value of online questionnaires in screening for CH (262). Wilbrink et al. developed a 142-item web based questionnaire to screen 437 patients with self-reported CH (262). An algorithm based on ICHD-II criteria was run automatically to determine the individual diagnoses (‘cluster headache’ versus ‘no cluster headache’) (262). Algorithm details were not provided. The questionnaire results were verified via semi-structured telephone interview by a medical student trained to diagnose CH (262). Two-hundred ninety-one patients were interviewed, of whom 243 were diagnosed with CH (sensitivity 57%; specificity 87%) (262). A subset of three questions identified from the full 142-item questionnaire had a moderate sensitivity (53.8%) and high specificity (88.9%) (262). Although this study included a large cohort of patients, it has several limitations (262). Firstly, the three-item questionnaire was not independently tested. Secondly, the length of the screening questionnaire could lead to a low response (142 items). Finally, the study did not include a control group (262). The current screening tools for the detection of CH have some drawbacks. These limitations could be overcome by the development of a novel screening tool to aid the diagnosis of CH.

Table 4.3. Existing screening tools for the detection of CH

Author	Screening tool	Study design	Participants	Findings	Advantages	Limitations
Chung et al. 2019 (263)	Eight-item screening tool administered in a tertiary centre	Questionnaire administered to first visit headache patients	42 CH 207 Migraine 73 TTH 18 P	At a cut-off score of >8points: Sensitivity 95.2% Specificity 96% PPV 76.9% NPV 99.3 %	Adequate sample size Control group included	1.Only one patient with CCH included 2.Possible selection bias due to enrolment in a tertiary headache centre
Wilbrink et al. 2013 (262)	Web-based 142-item questionnaire to diagnose CH for future large-scale studies	Phase 1: screening via website of self-reported CH patients and completion of questionnaire (an algorithm was used to determine the diagnosis) Phase 2: Questionnaire results tested via semi-structured telephone interview Phase 3: Construct a shorter questionnaire that predicts CH	Phase 1: 437 Phase 2: 291	Phase 2: 243/291 met the criteria for CH (Sensitivity 57.2%; Specificity 87.2%) Phase 3: three item-questionnaire was obtained	Adequate sample size Questionnaire results tested via semi-structured telephone interview	1.Three item-questionnaire not independently tested 2. Absence of control group 3. Lengthy screening questionnaire (142 items) 4. Algorithm details were not provided
Dousset et al. 2009 (258)	Three-item self-administered questionnaire to screen CH in tertiary centres	Questionnaire administered to already diagnosed patients	37 CH 59 Migraine	Sensitivity 78.4 % Specificity 100 %	Control group included	Small sample size (adequate sample size for the study was not determined)
Yoon et al. 2008 (260)	20-item self-administered questionnaire to diagnose migraine, TTH	The questionnaire results determined by an algorithm based on ICHD criteria were compared with those of	193	45 diagnoses of TACs by questionnaire 2 physician diagnoses of TACs	Questionnaire diagnosis was compared to physician diagnosis	1.Adequate sample size for the study was not determined 2.The types of TACs were not specified

	and TACs in a general population with headache	neurologists experienced in headache				3.Algorithm details were not provided
Kukava et al. 2007 (261)	20-item self-administered questionnaire in a general population with headache	The questionnaire results determined by an algorithm based on ICHD criteria were compared with those of neurologists experienced in headache	186	16 diagnoses of TACs by questionnaire 2 physician diagnoses of TACs	Questionnaire diagnosis was compared to physician diagnosis	1.Adequate sample size for the study was not determined 2.The types of TACs were not specified 3.Algorithm details were not provided 4.Study questionnaire was not provided
Fritsche at al. 2007 (259)	20-item self-administered questionnaire to diagnose migraine, TTH and TACs in a tertiary headache centre	The questionnaire results determined by an algorithm based on ICHD criteria were compared with those of neurologists experienced in headache	278	62 diagnoses of TACs by questionnaire 98 physician diagnoses of TACs	Questionnaire diagnosis was compared to physician diagnosis	1.Adequate sample size for the study was not determined 2.The types of TACs were not specified 3.Algorithm details were not provided 4.Study questionnaire was not provided
Torelli et al. 2005 (257)	16-item self-administered questionnaire to screen CH in tertiary centres	Questionnaire administered to already diagnosed patients	30 CH 21 Migraine 30 TTH	Performance of the whole questionnaire was not determined (only performance of individual items)	Control group included	1.Small sample size (adequate sample size was not determined) 2.Performance of the whole questionnaire was not determined (only performance of individual items) 3.Study questionnaire was not provided

Abbreviations: TACs: trigeminal autonomic cephalalgias; CH: cluster headache; TTH: tension-type headache; PSH: primary stabbing headaches; PPV: positive predictive value; NPV: negative predictive value

4.2.4 Existing visual tools for pain assessment

Several studies showed that visual tools could improve the communication during pain consultations (264-266). Photographic images (pain cards representing photographs), co-created by artists and patients with chronic pain in one-to-one workshops, were used during pain consultations (see Figure 4.1) (264). There might have been headache patients included in this study, but the authors used the umbrella term 'chronic pain conditions' without specifying exact diagnoses of the study participants (264). The photographic images were given to patients in the waiting room, they were asked to choose those that resonated with them and take it into their consultation and used it as they liked (264). The analysis of the post-consultation questionnaires, video footage of the consultations and transcripts showed that the images encouraged discussion of the emotional aspects of pain and led to more fruitful dialogue between patients and clinicians (264).

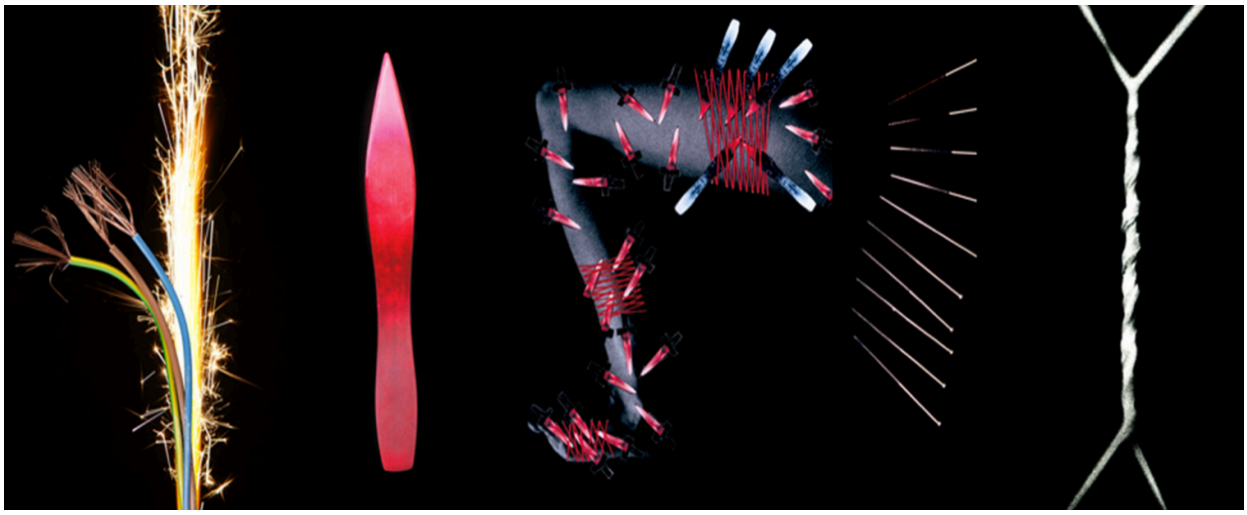


Figure 4.1. Photographic images (pain cards) used during pain consultations (264) (Reproduced with permissions from Padfield D. et al. Images as catalysts for meaning-making in medical pain encounters: a multidisciplinary analysis. Med Humanit 2018;44:74–81. doi:10.1136/medhum-2017-011415)

Drawings have been used in the assessment or diagnosis of headaches but this has been limited, so far, to paediatric settings (267-270). For instance, in one study children were asked to make drawings of their headache attacks (see Figure 4.2) (270). The usefulness of these drawings were tested in the differential diagnosis of migraine and non-migraine in children (270). Physicians who were not informed on the clinical diagnosis rated the drawings. The

drawings had high sensitivity (93.1 %) and high specificity (82.7%) and proved to be a useful diagnostic aid (270). Multiple pain assessment instruments have been developed so far including face pain scales, visual analogue scales, verbal and numerical rating scales for different clinical specialities (271) but images depicting different pain severities have never been used in headache studies.

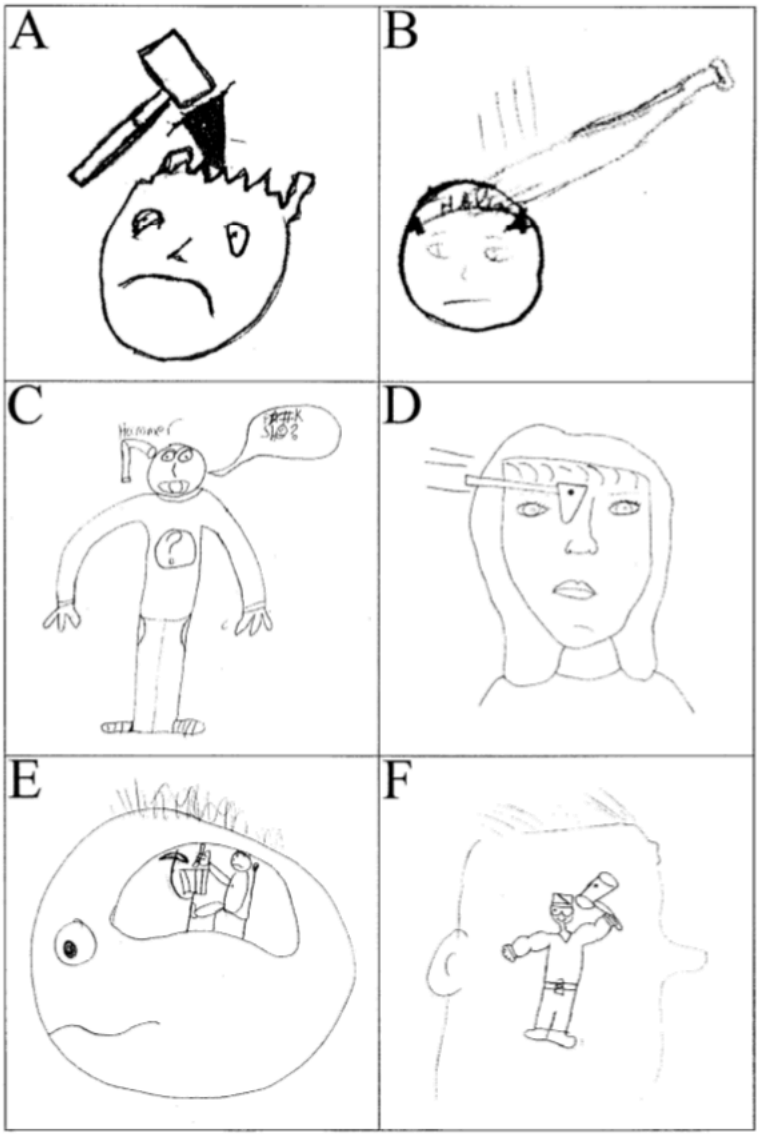


Figure 4.2. Drawings of children with headache depicting pounding pain (270) (Reproduced with permissions from Paediatrics, vol. 109, no.3, 2002 by the American Academy of Paediatrics)

4.3 Study objectives

Here, I outline the study objectives according to each study phase: (1) screening tool development; (2) pilot study, and (3) larger-scale study.

Phase I: Screening tool development

- To develop a screening tool to aid the diagnosis of CH

Phase II: Pilot study

- To assess the screening tool among patients with CH and migraine (control group)
- To verify that all questions are easily understood and to refine the screening tool

Phase III: Larger-scale study

- To assess the screening tool among patients with CH and migraine (control group)

4.4 Primary and secondary outcomes

In this section, I present the study's primary and secondary outcomes as follows:

Primary outcome

- To evaluate the performance of the tool as a whole in differentiating between CH and migraine (based on ICHD-3beta criteria) (272). This will be assessed by determining the total questionnaire score that best differentiates between CH and migraine

Secondary outcomes

- To determine the performance of each item in the tool. This will be assessed by calculating the sensitivity and specificity statistics
- To determine the performance of the images depicting pain in differentiating between CH and migraine. This will be obtained by calculating the sensitivity and specificity statistics
- To determine the association between test items

4.5 Methodology

In this section, I first present the study design comprised of three distinct phases: (1) screening tool development; (2) pilot study, and (3) larger-scale study. I continue with a section on statistical methodology including descriptive analysis, sensitivity and specificity statistics, receiver operating characteristics (ROC) analysis and correspondence analysis.

4.5.1 Study design

This is a prospective observational study, evaluating the performance of a novel 12-item self-administered questionnaire. Two patient groups were included: a study group (patients with CH) and a control group (patients with migraine). This research has received ethical approvals from the local University Research Ethics Committee (reference no: 1613/27.09.2016) and from the Health and Social Care Research Ethics Committee (HSC REC) (reference no: 16/NI/0269). The study consisted of a three-step procedure. Figure 4.3 depicts the study flow.

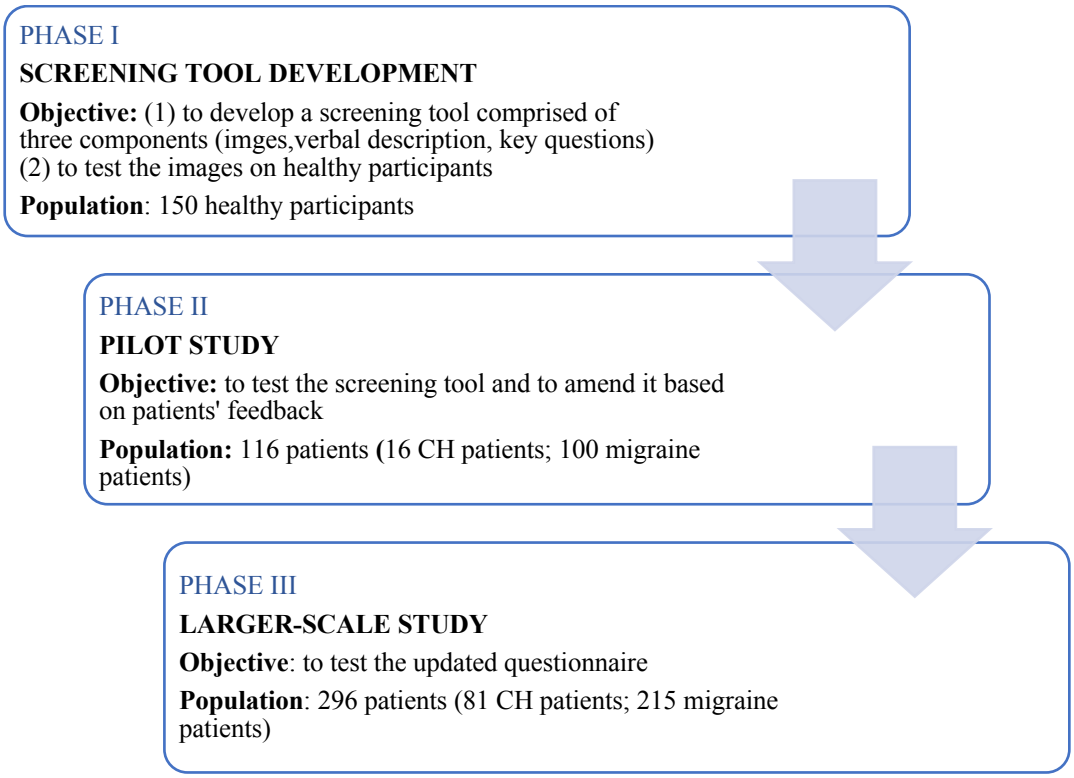


Figure 4.3. Study flow

4.5.1.1 Phase I: Screening tool development

The first phase of the study consisted of two main steps: (1) development of the three main components in the tool: images depicting headache pain, verbal description of pain, and key questions that could differentiate between CH and migraine; (2) to determine how healthy participants rated the images depicting headache pain.

Development of the main components in the tool

The screening tool is comprised of three main components: images depicting headache pain, verbal description of pain, and key questions that could differentiate between CH and migraine. There are two things that lay at the inception of this screening tool. Firstly, a small interview study conducted by FA in our research team, in which CH and migraine patients were interviewed and a set of images was used to identity their symptoms (273). Secondly, the ARTe Cluster Project, that collects and exhibits artistic renditions of CH to raise awareness of the huge impact the disease has on CH sufferers (274, 275). A range of images that depict headache pain in different ways were used, inspired on real life pictures and images frequently used on CH websites (see Figure 4.4) (275). The same person sketched six drawings as I wanted all the images to have similar characteristics (colour saturation and chromatic range) in order to avoid the influence of colour on attentional bias (276). All images were printed in black-and-white on the same size.

Figure 4.4. Images depicting headache pain illustrating different severities

The ICHD-3 criteria and the patients' description of pain in the CHIPS study were used to determine the verbal description of pain. The verbal description of pain included categories such as nature of pain, intensity, description of pain, associated symptoms, and behaviour during the attacks. The key questions guiding the history taking were provided by 10 UK based headache specialists, members of the British Association for the Study of Headache (BASH). Expert designed questionnaires are often used in pain studies (277, 278). The headache experts were invited to participate via e-mail. They were asked to provide in writing (via e-mail) between three and five questions that could differentiate between CH and migraine during a

clinical consultation. The most asked questions provided by the headache experts were included in the novel screening tool.

Assessment of images on healthy participants

The screening tool was tested on 150 healthy participants to determine if the images depict a range of pain severities. These were people without a history of headaches or chronic pain conditions. The participants were employees of the National Health Service (NHS) in Hull and the University of Hull (UK). The healthy participants were asked to rate each image as showing mild, moderate, severe or excruciating pain. They had the option to choose multiple answers or not to answer (see Figure 4.5).

Please answer the following questions:

(There is no right or wrong answer. Please rate all the images. You can choose more than one image for each answer but you cannot choose the same image for more than one answer)

Which image/s, in your opinion, represent/s:

1. **excruciating pain**? _____
2. **severe pain?** _____
3. **moderate pain?** _____
4. **mild pain?** _____

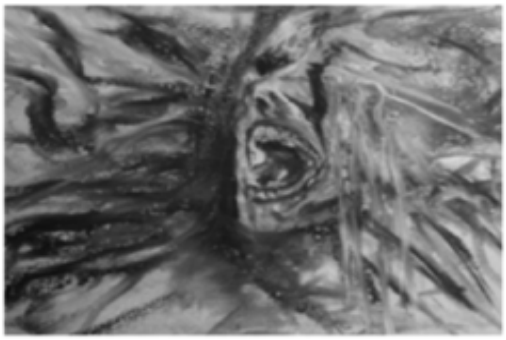


Image 1

Image 2

Image 3

Image 4

Image 5

Image 6

Figure 4.5. Questionnaire with images depicting headache pain assessed on healthy participants

4.5.1.2 Phase II: Pilot study

The screening tool was tested on 116 patients (16 patients with CH, 100 patients with migraine). Patients received a prior diagnosis of CH or migraine (control group) based on the ICHD-3b criteria before they were invited to participate (272). The patients were recruited prospectively from a tertiary headache centre in the North of England between February-May 2017. All patients provided informed consent. The patients were asked to complete the questionnaire and to provide feedback on the question clarity. The questionnaire was updated based on patients' feedback.

4.5.1.3 Phase III: Larger-scale study

The refined screening tool was tested on a larger-scale study that included 296 patients (81 patients with CH; 215 patients with migraine). The patients were recruited prospectively from a tertiary headache centre between October 2017-March 2019. The patients completed the questionnaire unaided and were asked to provide a single answer for each question. Patients with dual diagnosis, CH and migraine were excluded from the study.

4.5.2 Statistical methodology

In this section, I outline the statistical methods used to analyse the dataset including descriptive analysis of the test scores, sensitivity and specificity statistics and ROC curve statistics.

4.5.2.1 Descriptive analysis of the test scores

For the purpose of statistical analysis, the test scores were coded numerically using integers and the variables were given abbreviated names as defined in Table 4.4. The frequency distribution (counts and percentages) of the categories within each of the 12 variables used to evaluate the performance of the screening tool were computed for each group of patients. Higher scores were given for test items characteristic for CH. A dichotomous scale (no=0; yes=1) was used for the test items with binary response (restlessness, excruciating agony, headache at specific times, strictly unilateral pain, ipsilateral cranial autonomic symptoms). Test items for severity of pain were coded as follows: image preference (f = 1 (least severe); a = 2; c = 3; b = 4; e = 5; d = 6 (most severe)) (39), pain scale (scores from zero to ten) and intensity of pain (mild = 1; moderate = 2; severe = 3; very severe = 4; excruciating = 5). The description of pain 'red hot poker in the eye', usually attributed to CH (236) was coded with 1

whilst ‘pounding heart in the head/other’ coded with 0. ‘Stabbing/burning’ pain that usually characterises CH (279) was coded with 3 while ‘pressure’ was coded with 2 and ‘throbbing/other’ with 1. The attack duration ≤ 3 hours, a feature of CH was coded with 1, whilst the attack duration > 3 hours was coded with 0. A total score was determined by adding up the scores for the 12 items in the screening tool (263). The total score was analysed to evaluate the overall performance of the screening tool. Table 4.5 shows that the minimum possible total score = 3, and the maximum possible total score = 32. The descriptive statistics (mean ± 95% CI) of the total score were compared between each group of patients. The mean scores for each group were assumed to be significantly different from each other if their 95% CI did not overlap (280).

Table 4.4. Variables measured with the 12-item screening tool

Question	Variable	Coded test scores
1. Please choose one image that best illustrates the most severe headache you have experienced	Image preference	f = 1 (least severe); a = 2; c = 3; b = 4; e = 5; d = 6 (most severe)
2. Please mark with an X the intensity of your pain on the scale below	Pain scale	Scores from zero to ten
3.Please choose only one option from the following list that describes your headaches	Intensity	Mild = 1; Moderate = 2; Severe = 3; Very severe = 4; Excruciating = 5
4.Please choose only one option from the following list that describes your headaches	Nature of pain	Throbbing/Other = 1; Pressure = 2; Stabbing/Burning = 3
5. Please choose only one option from the following list that describes your headaches	Description of pain	Red hot poker in the eye = 1; Pounding heart in the head/Other = 0
6. Do you feel restless during the headache attack?	Restlessness	No = 0; Yes = 1
7. Is the pain 'excruciating agony'?	Excruciating agony	No = 0; Yes = 1
8. Does the pain wake you up from sleep the same time each night/ or attack comes at a specific time of the day?	Headache at specific times	No = 0; Yes = 1
9. Is the pain strictly on one side?	Strictly unilateral pain	No = 0; Yes = 1
10.Ipsilateral cranial autonomic symptoms (e.g. red watery eyes and/or runny nose?)	Ipsilateral cranial autonomic symptoms	No = 0; Yes = 1
11. How long does the most severe pain last for when treated?	Treated attack duration	> 3 hours = 0; ≤ 3 hours = 1;
12. How long does the most severe pain last for when untreated?	Untreated attack duration	> 3 hours = 0; ≤ 3 hours = 1;

Table 4.5. Computation of total score

Variable		Minimum	Maximum
1	Image preference	1	6
2	Pain scale	0	10
3	Intensity	1	5
4	Nature of pain	1	3
5	Description of pain	0	1
6	Restlessness	0	1
7	Excruciating agony	0	1
8	Headache at specific times	0	1
9	Strictly unilateral pain	0	1
10	Ipsilateral cranial autonomic symptoms	0	1
11	Treated attack duration ≤ 3h	0	1
12	Untreated attack duration ≤ 3h	0	1
Total score		**3**	**32**

4.5.2.2 Correspondence analysis of the test scores

The statistical associations between the six image preferences and other categorical variables were explored, in order to determine which image preference was most closely associated with each categorical variable. The chi-square test is commonly used by medical researchers to analyse the associations between categorical variables (281). However, the chi-square test is an inferior method because it can only determine if the observed associations between the categories deviate from the associations expected by random chance (indicated by the p-value). This is not very useful information because a p-value does not measure the importance or strength of the relationship between variables. According to the official statement issued by the American Statistical Association, a p-value should not be used to draw scientific conclusions or make policy decisions (282). The method used to explore the statistical associations between the six image preferences and other categorical variables in the current study was correspondence analysis. This multivariate method has previously been applied by other medical researchers to explore the associations between categorical variables, and is particularly useful in epidemiological studies (283-285).

Correspondence analysis which is an exploratory method was applied to open a window using a graphic visualization to explore the associations between the categorical variables in

the screening tools. The high-dimensional information in each cross-tabulation was broken down into two factors (termed Component 2 versus Component 1) and plotted as points on two constructed axes called a correspondence map. The two components in the correspondence map summarized the associations between the categories. The geometric orientation of the points in the correspondence map reflected the relative similarities and differences between the categories. Categories that were most closely associated with each other were represented by clusters of points located in near proximity. The points that were closest together were the most positively correlated. The points that were the farthest apart were the most negatively correlated.

Correspondence analysis was used to determine association between the test items. The 'rule of thumb' is that the sample size should be at least five times the number of cells in the cross-tabulation (286). For example, in a correspondence analysis to explore the associations between 'image preferences' (six categories) and the 'pain scale' (10 categories) the minimum sample size should be 6 x 10 x 5 = 300.

4.5.2.3 Sensitivity, specificity statistics and the ROC analysis

The sample size for sensitivity and specificity statistics was calculated to get a reasonable accurate estimate of the sensitivity and specificity of the tool in predicting CH. The tool is expected to have a sensitivity and specificity of 90%. It is required to obtain an estimate that is correct to within 7% either side of this figure. Using a 95% confidence level, it is calculated that a minimum of 71 subjects are required. Estimates of sensitivity and specificity are based only on the group with and without CH respectively, and thus 71 subjects with CH and 71 subjects without CH are required, a minimum sample size of 142 subjects.

The statistical analysis was conducted using the frequencies of the responses to the 12-item screening tool that were administered to two groups of patients. Sensitivity, specificity, false positive rate (FPR), false negative rate (FNR), positive predictive value (PPV) and negative predictive value (NPV) were determined for the eight items with dichotomous responses. Table 4.6 shows how eight of the test items in the screening tool with dichotomous responses were coded in binary format (i.e. 0 or 1).

Table 4.6. Test items with dichotomous responses

Test item	Scores
Restlessness	Yes = 1; No = 0
Excruciating agony	Yes = 1; No = 0
Headaches at specific times	Yes = 1; No = 0
Strictly unilateral pain	Yes = 1; No = 0
Ipsilateral cranial autonomic symptoms	Yes = 1; No = 0
Description of pain	Red hot poker = 1; Pounding heart/other = 0
Treated attack duration	≤ 3 h = 1; > 3 h = 0
Untreated attack duration	≤ 3 h = 1; > 3 h = 0

The responses to four test items in the screening tool were ordinal variables, consisting of three or more ranked responses. Tables 4.7 shows how the ordinal responses were coded numerically in rank order from 0 to 10.

Table 4.7. Test items with ordinal responses

Test item	Scores
Image preference	f = 1; a = 2; c = 3; b = 4; e = 5; d = 6
Visual analogue pain scale	scores from zero to ten
Intensity of pain	mild = 1; moderate = 2; severe = 3; very severe = 4; excruciating = 5
Nature of pain	throbbing/other = 0; pressure = 1; stabbing = 2

ROC analysis was estimated for these four items. The ROC curve was a plot of the true positive rate (sensitivity) against the false positive rate (1 - specificity) based on three or more scores for a diagnostic test, and reflected the tradeoff between sensitivity and specificity (287). The purpose of constructing ROC curves was to estimate how accurately each set of test item scores separated the patients into two groups (i.e. patients with CH versus patients with migraine). The area under the curve indicated the accuracy of the test. An area of 1.0 represented a perfect test whilst an area of 0.5 represented a worthless test. The criteria used to estimate the accuracy of each test item was 0.90-1.0 = excellent; 0.80-0.90 = good; 0.70-.080 = fair; 0.60-0.70 =

poor; 0.50-0.60 = very poor (288). The ROC curve also permitted the identification of a cut-off test score that best distinguished between patients with CH and patients with migraine. This cut-off test score was indicated by the inflection point on the ROC curve that was closest to the top left corner. The closer the ROC curve followed the 45-degree diagonal through the ROC space (the reference line), then the less accurate was the test curve. Gender segregated analysis was also performed by separating the data set into males and females. For females, class balancing was performed to equalise the number of occurrences of CH and migraine. For males, balancing was not required as the data set is approximately balanced.

The total scores for the 12 items in the screening tool for CH and migraine were computed to evaluate the overall performance of the tool. Descriptive statistics (mean and 95% confidence intervals) and ROC curve statistics were computed to determine how the total scores could be interpreted to distinguish between patients diagnosed with CH, and patients diagnosed with migraine.

4.6 Results

In this section, I first present the results from the phase I of the study, including the results on how health participants rated the images depicting headache pain. I continue presenting the verbal descriptions of pain and the key questions included in the screening tool. Secondly, I present findings from the pilot study on patients with CH and migraine and their feedback on the questionnaire. Lastly, I show the refined screening tool and results from the larger-scale study on patients with CH and migraine.

4.6.1 Phase I: Screening tool development

Here, I present findings on how healthy participants rated the images illustrating different pain severities, followed by presenting the verbal descriptions of pain and the key questions able to differentiate between CH and migraine provided by headache experts.

4.6.1.1 Assessment of images on healthy participants

One hundred and fifty healthy participants were included in the study. The findings are that the participants agreed that the six images in the screening tool are depicting a range of pain severities from mild to excruciating (see Table 4.8, Figure 4.6). Most participants rated ‘image 1’ (*n*=131/150, 87%) and ‘image 5’ (*n*=93/150; 63%) as ‘excruciating’. Twenty-one percent (*n*=32/150) of the participants chose not to rate ‘image 5’. I assume that the level of pain

depicted by ‘image 5’ is not clear to the participants. Therefore, ‘image 1’ seems to be more representative for expressing an excruciating level of pain. ’Image 2’ was rated as either moderate (*n*=60/150; 40%) or severe (*n*=59/150; 39%). The participants rated ‘image 3’ (*n*=93/150; 62%), ‘image 4’ (*n*=88/150; 58%) and ‘image 6’ (*n*=129/150; 86%) as showing severe, moderate and mild level of pain respectively.

Table 4.8. Image rating according to severity

Image number	**Image rating according to severity** (number of participants)				
	Mild	Moderate	Severe	Excruciating	No rating
Image 1	0	0	1	131	18
Image 2	9	60	59	4	18
Image 3	2	18	93	25	12
Image 4	26	88	24	4	8
Image 5	0	3	22	93	32
Image 6	129	15	1	0	5

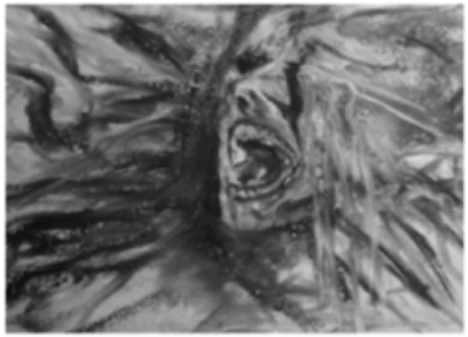
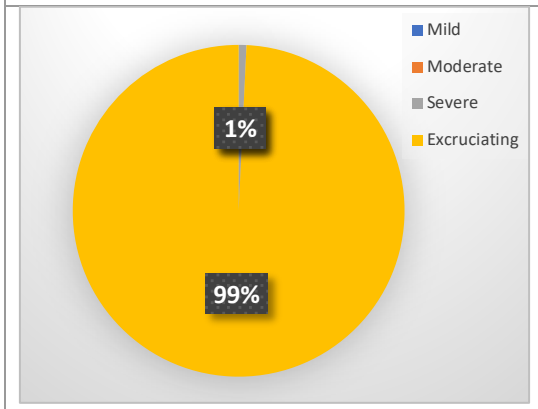
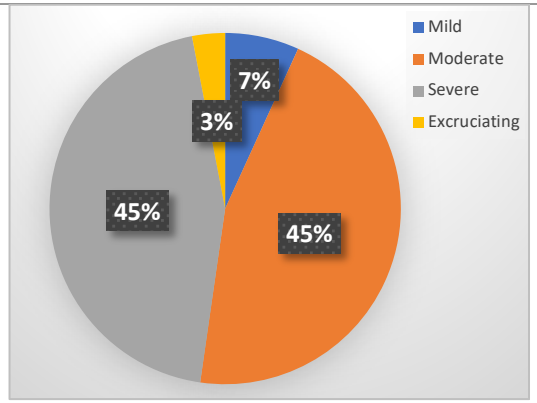
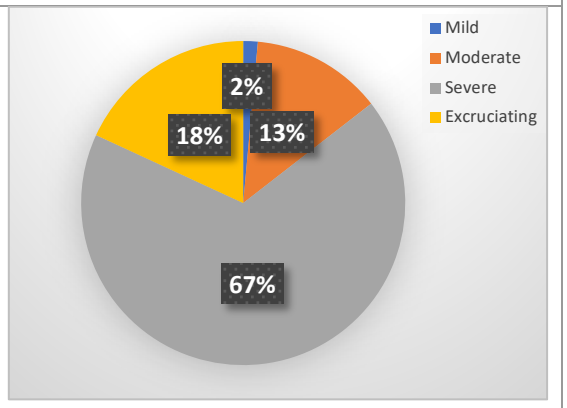
Image 1	Image 2	Image 3
		
Answer distribuition (%)		
		

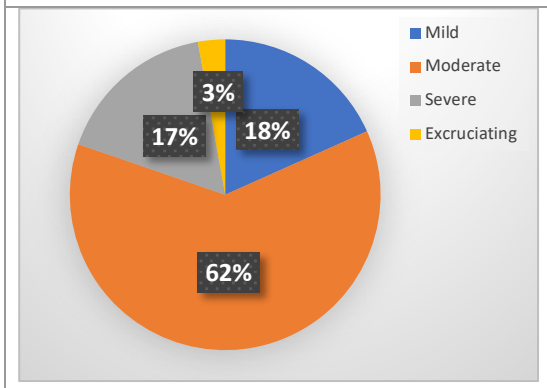
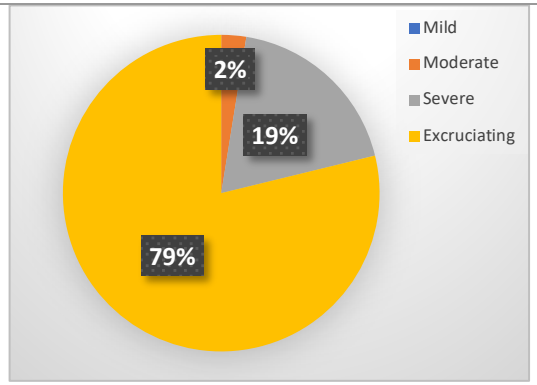
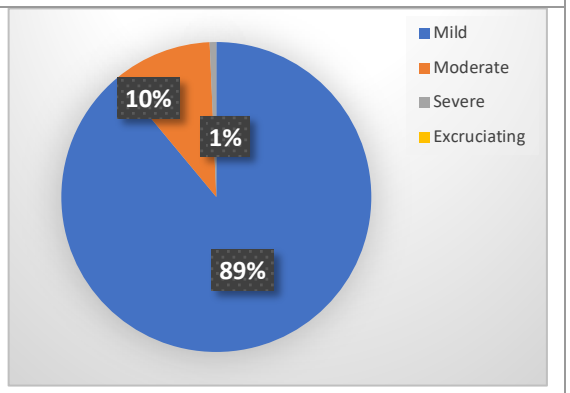
Image 4	Image 5	Image 6
		
Answer distribution (%)		
		

Figure 4.6. Images depicting headache pain and the answer distribution

4.6.1.2 Verbal descriptions of pain

The ICHD-3beta (272) and patients' description of pain in the CHIPS study (289, 290) were used to design the verbal description of headache attacks captured in this study. According to ICHD-3beta, CH is described as severe/very severe pain often associated with restlessness while migraine has a pulsating quality of moderate or severe intensity and it is aggravated by routine physical activity. The CH pain is often described as a 'red hot poker in the eye' of intense severity (236) or 'the most excruciatingly pain' (289). Figure 4.7 shows five categories included in the screening tool such as nature of pain, pain intensity, description of pain, associated cranial autonomic symptoms and preference (desire to lie down/restlessness). Patients were asked to choose a single answer from each category.

Below, I show examples of anonymized patient quotes from the CHIPS study:

> It's like the most excruciatingly pain in my head that feels like somebody is banging a nail into it (…) it was like someone banging a nail into the back of my head. I can only describe it as a ball of fire going around this side of my head and into my cheek, into my ear (…) and it's absolutely effing excruciating. (R11, female 40, ECH)

> It just feels like there's something in your head that's going to explode, it's like everything in this side of your head is red hot, like you've got a red-hot poker in your eye (…) and somebody's just screwing it around like that and it just feels like your head's just going to explode. (R6, male 65, CCH)

> It's like there's two people, one's stabbing a red-hot poker in my eye while the other one's got a hammer and banging it on side of my face. (R8, female 46, ECH)

a). **Nature**: Throbbing / Pulsating / Stabbing / Cutting / Burning pain / Pressure / Any other

b). **Intensity**: Mild / Moderate/ Severe / Very severe / Excruciating/ Any other

c). **Description**: Red hot poker in the eye / Pounding heart in the head /Any other

d). **Associated symptoms of red watery eyes and/or runny nose:** i) YES; ii) NO

e). **Preference**: i) Desire to lie down or sit still; ii) Restlessness, need to move, rocking

Figure 4.7. Verbal descriptions of headache attacks

4.6.1.3 Key questions that could differentiate between CH and migraine

Ten UK based headache specialists, members of the British Association for the Study of Headache (BASH) provided questions that, in their opinion, are able to differentiate between CH and migraine. Table 4.9 shows the questions provided by the headache experts in the order of frequency. Thirty-five questions were provided. One of the headache experts provided six questions, two experts delivered four questions each and other seven specialists provided three questions each.

Table 4.9. Questions provided by the headache experts that could differentiate between CH and migraine

Questions	Number of headache experts
Is restlessness present during the attacks?	9
How long does the most severe pain last for?	5
Is the pain strictly unilateral?	5
Are attacks coming on a specific time of the day or night?	4
Is the pain excruciating or like an excruciating agony?	4
Are there any associated cranial autonomic symptoms?	2
Is alcohol a trigger?	2
Is the pain worse than childbirth?	1
How frequent are the headaches?	1
How long does it take for the pain to reach the maximum intensity?	1
Are there any suicide thoughts during the attacks?	1

The five most asked questions were included in the new screening tool. The questions required yes or no answers, except the question regarding the pain duration where patients had to report the length of pain (see Figure 4.8).

a. Do you feel restless during the headache attacks? YES/NO
b. How long does the most severe pain last for? ___
c. Is the pain strictly on one side with either one or all of these symptoms (red eye, eye and nose runs)? YES/NO
d. Does the pain wake you up from sleep the same time each night/or are the attacks coming at a specific time of the day? YES/NO
e. Is the pain 'excruciating agony'? YES/NO

Figure 4.8. Key questions included in the screening tool

Figure 4.9 depicts the screening tool comprised of the three main components: six visual images, verbal descriptions, and key questions that could differentiate between CH and migraine.

Participant no: __
Male/Female
Age: ____
Diagnosis: Migraine /Cluster Headache; Episodic/Chronic

❶ IMAGES. Please choose one image that best illustrates the most severe headache you have experienced:

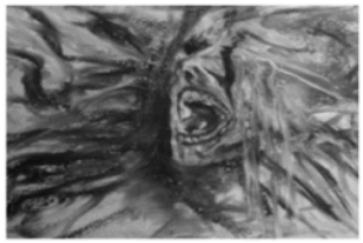


Image 1


Image 2


Image 3


Image 4


Image 5


Image 6

❷ KEY WORDS. Please choose one key word from each category that best describes your headaches/associated symptoms during headache:

a. Nature: Throbbing / Pulsating / Stabbing / Cutting / Burning pain / Pressure / None of these

b. Intensity: Mild / Moderate/ Severe / Very severe / Excruciating/ None of these

c. Description: Red hot poker in the eye / Pounding heart in the head /None of these

d. Associated symptoms of red watery eyes and/or runny nose
   i) YES
   ii) NO

e. Preference: i) Desire to lie down or sit still
   ii) Restlessness, need to move, rocking

❸ KEY QUESTIONS. Please answer the following questions:

1. Do you feel restless during the headache attacks? YES/NO
2. How long does the most severe pain last for? _____
3. Is the pain strictly on one side with either one or all of these symptoms (red eye, eye or nose runs)? YES/NO
4. Does the pain wake you up from sleep the same time each night/or attacks coming at a specific time of the day? YES/NO
5. Is the pain 'excruciating agony'? YES/NO

Figure 4.9. Screening tool for CH

4.6.2 Phase II: Pilot study

In this section, I first present the demographic profile of the study population included in the pilot study. I continue with outlining patients' feedback on the screening questionnaire and how the questionnaire was refined. I conclude with a section on the descriptive analysis of the findings.

4.6.2.1 Demographic profile of the study population

One hundred and sixteen patients participated: 100 patients with migraine (93 patients with chronic migraine; 7 patients with episodic migraine) and 16 patients with CH (9 patients with chronic CH; 7 with episodic CH). The patients were recruited between February-May 2017. Eighty-six percent (86%) of the patients with migraine are females and 14% males with a mean age of 44 (95% CI 41.8; 46.3) (males *n*=14/100; females *n*=86/100;). Nineteen percent (19%) of patients with CH were females and 81% males with a mean age of 48 (95% CI 40.6;55.3) (females *n*=3/16; males *n*=13/16) (see Table 4.10).

Table 4.10. Demographic profile of the study population

Variable	**Migraine**	**CH**
Number of participants	100	16
Number of male/female	14/86	13/3
Number of episodic/chronic	7/93	7/9
Gender ratio (male/female)	1/6	4.3
Age in years: mean (95% CI)	44 (41.8; 46.3)	48 (40.6; 55.3)

4.6.2.2 Patients' feedback on the screening tool

Patients with migraine in the pilot study raised concerns regarding the question comprehension. It was unclear if 'headaches' referred to mild headaches or migraine attacks. Some patients who experienced attacks of different pain severities had difficulties rating the intensity of their attacks (e.g. mild, moderate, severe, very severe, excruciating). To overcome these limitations, the updated version of the tool was customised based on the diagnosis (e.g. 'Please chose only one image that best illustrates your cluster headache attacks' versus 'Please chose only one

image that best illustrates your migraines'). Questions regarding the behaviour during headaches were found to be repetitive (e.g. Preference: desire to lie down/restlessness, need to move, rocking' versus 'Do you feel restless during the headaches?'). Hence, the new version of the screening tool was updated accordingly. It was unclear if the question regarding the duration of pain referred to treated or untreated attacks. The sequence of images was modified in the new screening tool in order to avoid a possible influence of the position of images on the choices made by patients (291). The image labels were changed from numbers to letters to avoid the same (292). Table 4.11 shows the amendments of the screening tool based on patients' feedback. A pain scale was added to the refined screening tool that will facilitate a comparison between the image chosen and the intensity of pain (see Figure 4.10).

Table 4.11 Screening tool amendments based on patients' feedback

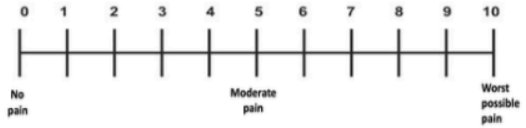
Patients' feedback	**Screening tool amendments**
It was unclear if the term 'headache' referred to the mild headaches or migraine attacks	The tool was customised based on the two diagnosis: CH and migraine (see Figure 4.10 and Appendix 4)
Patients found the questions regarding the behaviour during attacks as being repetitive (e.g. 'Preference: desire to lie down/restlessness, need to move, rocking' and 'Do you feel restless during the headaches?').	The two questions were replaced with: 'Do you feel restless during the attacks'? YES/NO'
It was unclear if the question regarding the duration of pain referred to treated or untreated attacks	The duration of treated and untreated attacks was added to the tool
Some patients that experience attacks with different severities had difficulties rating the pain intensity	The tool was customised based on the two diagnosis: CH and migraine (see Figure 4.10 and Appendix 4)

Male / Female
Age__

Cluster Headache
Episodic / Chronic

1 Please choose only ONE image that best illustrates your cluster headache attacks

2 Please mark with an X the intensity of your cluster headache attacks on the scale below



3 Please choose only ONE option from each category that best describes your cluster headache attacks

Intensity	Mild	Moderate	Severe	Very Severe	Excruciating
Nature	Pressure	Throbbing	Stabbing	Burning	Other_____
Description	Red hot poker in the eye		Pounding heart in the head		Other_____

4 Please answer the following questions

A. Do you feel restless (pace the floor or rock your body) most of the time during your cluster headache attacks?

YES NO

B. When you have a cluster headache attack is the pain 'excruciating agony' most of the time?

YES NO

C. Do your cluster headache attacks come at specific times?

YES NO

D. Are your cluster headache attacks located just on one side?

YES NO

E. Are there any associated symptoms (one or more of the following: red eyes, watery eyes, droopy eye, runny nose, facial sweating, fullness in the ear) on the same side as the pain?

YES NO

F. How long does a cluster headache attack last for?

With medication ____ Without medication____

Figure 4.10. Refined screening tool for CH

4.6.2.3 Descriptive analysis of the findings

The headache characteristics of the two groups of patients are summarised in Table 4.12. Two-thirds of patients with CH (69%) and half of the patients with migraine (52%) chose 'image 1' as being illustrative for their headache attacks. 'Image 1' was rated by 89% of the healthy participants as exhibiting an 'excruciating' level of pain. Similarly, three-quarters of patients with CH (75%) and almost half of the patients with migraine (47%) reported excruciating headache intensity. Over 80% of patients in the CH group described their headache as 'red hot poker in the eye', whereas this description was given by 20% of the migraine group. The migraine group gave 'pounding heart' (54%) as the most common response to the question on the nature of pain, whilst half of the CH group reported 'stabbing' pain (50%).

The occurrence of the cranial autonomic symptoms (red eye/eye or nose runs) was higher in the CH group. This occurred in 87% of this group, compared to less than half of the migraine group (47%). The two groups had different preferences about how they behave during the headache attacks. Over 80% of the migraine group had a desire to lie down, whilst over 80% of the cluster headache group were restless. The CH group were more likely to experience unilateral headaches (81%) and also more likely to have attacks at the same time of the day (75%). Three quarters of patients with CH had attacks at the same time of the day, compared to 38% of the migraine group.

Table 4.12. Headache characteristics classified by diagnosis

Variable	Category	Migraine (n=100)	CH (n=16)
		% within diagnosis	
Image preference	Image 1	52 (52%)	11 (69%)
	Image 2	20 (20%)	1 (6%)
	Image 3	21 (21%)	3 (19%)
	Image 4	4 (4%)	1 (6%)
	Image 5	2 (2%)	0 (0%)
	Image 6	1 (1%)	0 (0%)
Nature of pain	Burning pain	6 (6%)	0 (0%)
	Pressure	17 (17%)	5 (31%)
	Pulsating	12 (12%)	0 (0%)
	Stabbing	24 (24%)	8 (50%)
	Throbbing	35 (35%)	2 (13%)
	Other	6 (6%)	1 (6%)
Intensity of pain	Mild	0 (%)	0 (%)
	Moderate	8 (8%)	0 (0%)
	Severe	22 (22%)	1 (6%)
	Very severe	23 (23%)	3 (19%)
	Excruciating	47 (47%)	12 (75%)
Description of pain	Pounding heart	54 (54%)	3 (19%)
	Red hot poker	20 (20%)	13 (81%)
	Other	26 (26%)	0 (0%)
Cranial autonomic symptoms	No	53 (53%)	2 (13%)
	Yes	47 (47%)	14 (87%)
Preference	Desire to lie down	85 (85%)	3 (19%)
	Restlessness	15 (15%)	13 (81%)
Restlessness during headaches	No	43 (43%)	1 (6%)
	Yes	57 (57%)	15 (94%)
Duration of pain mean (95% CI)		28.2 (22.1; 34.4)	2.2 (1.7; 2.8)
Strictly unilateral pain	No	53 (53%)	3 (19%)
	Yes	47 (47%)	13 (81%)

Attacks at the same time	No	62 (62%)	4 (25%)
	Yes	38 (38%)	12 (75%)
Excruciating agony	No	25 (25%)	1 (6%)
	Yes	75 (75%)	15 (94%)

4.6.3 Phase III: Larger-scale study

Here, I first present a section on the descriptive analysis of the study sample and test scores. I continue outlining the descriptive analysis of the results and association between test items determined with the correspondence analysis. I conclude with a section on the findings on both the overall performance of the screening tool and individual test items.

4.6.3.1 Description of the sample

The sample consisted of 296 patients, classified into two groups, the case group and the control group. The case group consisted of patients diagnosed with CH (*n*=81, 27.4%) of whom 45 patients with chronic CH (55.6%) and 36 with episodic CH (44.4%). The control group consisted of patients with migraine (*n*=215, 72.6%) of whom 123 were patients with chronic migraine (57.2%) and 92 patients with episodic migraine (42.8%).

Table 4.13 compares the gender distributions of the 296 patients classified by diagnosis. Females were the most frequent gender (70.9%). The most frequent diagnosis among the 210 females was chronic migraine (51.4%) followed in order of frequency by episodic migraine (34.3%); chronic CH (10.0%) and episodic CH (4.3%). The diagnoses among the 86 male patients did not follow the same pattern in order of frequency: episodic CH (31.4%) followed by chronic CH (27.9%); episodic migraine (23.3%) and chronic migraine (17.4%). The male:female ratio in the CH group was 1.7:1 and in the migraine group was 1:5.1.

Table 4.13 Gender distribution of patients with CH and migraine

Gender	Proportion	Diagnosis				Total
		Case group		Control group		
		Chronic CH (n = 45)	Episodic CH (n = 36)	Chronic migraine (n = 123)	Episodic migraine (n = 92)	
Female	Frequency	21	9	108	72	210
	% within diagnosis	10.0%	4.3%	51.4%	34.3%	100.0 %
Male	Frequency	24	27	15	20	86
	% within diagnosis	27.9%	31.4%	17.4%	23.3%	100.0 %

The ages of the patients ranged from 18 to 79 years (mean = 43.8; 95% CI = 42.3; 45.6). Figure 4.11 compares the mean age and 95% CI of the four groups of patients classified by diagnosis. Patients with CH had a mean age of 46.06 (95% CI = 43.18; 48.94) and patients with migraine a mean age of 42.93 (95% CI = 41,02; 44.83). The ages of the patients diagnosed with episodic migraine tended to be lower than the ages of the patients diagnosed with chronic CH, chronic migraine, and episodic CH.

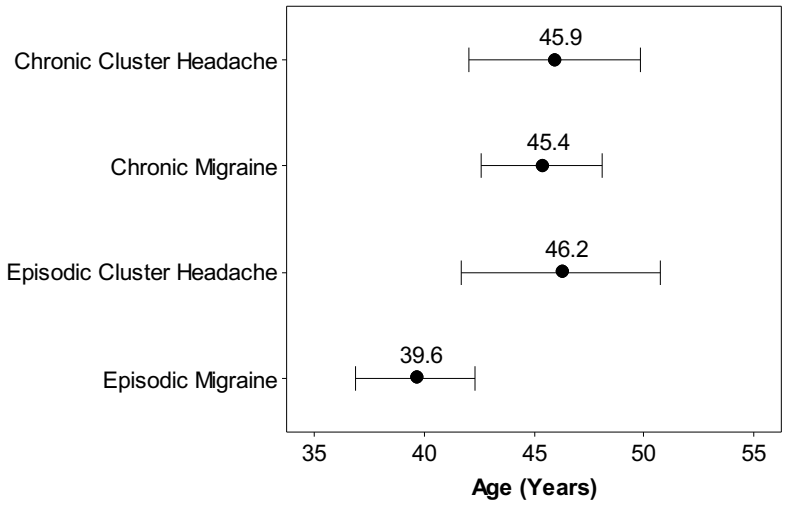


Figure 4.11. Mean age ± 95% CI of patients classified by diagnosis

4.6.3.2 Descriptive analysis of test scores

Table 4.14 summarizes the frequency distributions of the ordinal test scores classified by diagnosis. The 'image preference' with the highest frequency was 'image d' for chronic CH (60.0%) and episodic CH (63.9%); whereas 'image c' (26.0%) and 'image d' (25.2%) were the highest frequencies for chronic migraine. Most patients with episodic migraine tended to prefer 'image a' (27.2%) and 'image b' (22.8%).

The 'pain scale' with the highest frequency was 10 for chronic CH (55.6%) and episodic CH (72.2%); whereas a 'pain scale' of 8 (31.7%) and 9 (25.2%) were the highest frequencies for chronic migraine. Most patients with episodic migraine tended to report a 'pain scale' of 7 (16.3%) or 8 (35.9%).

The 'intensity of pain' with the highest frequency was 'excruciating' for chronic CH (75.6%) and episodic CH (91.7%); whereas severe (34.1%) and very severe (32.5%) were the highest frequencies for chronic migraine. Most patients with episodic migraine also tended to report 'intensity of pain' as severe (35.9%) or very severe (34.8%).

The 'nature of pain' with the highest frequency was 'stabbing/burning' for chronic CH (68.9%) and episodic CH (66.7%); whereas 'throbbing' (43.1%) was the highest frequency for chronic migraine. Most patients with episodic migraine also tended to report the 'nature of pain' as 'throbbing' (37%) or 'pressure' (38%).

The untreated and treated attack duration in the migraine group was more than three hours (82.9% treated attacks, and 100% untreated attacks).

Table 4.14. Frequency distribution of ordinal test scores

Variable	Category	% within Diagnosis			
		Case group		Control group	
		Chronic CH (n = 45)	Episodic CH (n = 36)	Chronic migraine (n = 123)	Episodic migraine (n = 92)
Image preference	a	6.7	2.8	10.6	27.2
	b	13.3	8.3	20.3	22.8
	c	2.2	5.6	26.0	20.7
	d	60.0	63.9	25.2	10.9
	e	11.1	5.6	10.6	4.3
	f	6.7	13.9	7.3	14.1
Pain scale	1	0.0	0.0	0.0	0.0
	2	0.0	0.0	0.0	0.0
	3	0.0	0.0	0.0	3.3
	4	0.0	0.0	0.8	3.3
	5	2.2	0.0	0.8	5.4
	6	0.0	0.0	6.5	4.3
	7	6.7	0.0	15.4	16.3
	8	4.4	2.8	31.7	35.9
	9	31.1	25.0	25.2	15.2
	10	55.6	72.2	19.5	16.3
Intensity of pain	Mild	0.0	0.0	0.0	2.2
	Moderate	0.0	0.0	11.4	16.3
	Severe	15.6	0.0	34.1	35.9
	Very severe	8.9	8.3	32.5	34.8
	Excruciating	75.6	91.7	22.0	10.9
Nature of pain	Throbbing	22.2	13.9	43.1	37.0
	Pressure	8.9	19.4	28.5	38.0
	Stabbing/ burning	68.9	66.7	28.5	25.0
Treated attack duration	≤ 3 hours	100.0	100.0	17.1	31.5
	> 3 hours	0.0	0.0	82.9	68.5
Untreated attack duration	≤ 3 hours	100.0	100.0	0.0	0.0
	> 3 hours	0.0	0.0	100.0	100.0

Table 4.15 summarizes the frequency distributions of the test scores with binary responses classified by diagnosis. The 'description of pain' with the highest frequency was 'red hot poker in the eye' for patients diagnosed with chronic CH (57.8%) and episodic CH (80.6%), whereas 'pounding heart in head' was the highest frequency for patients diagnosed with chronic migraine (82.9%). Most patients with episodic migraine also tended to report the 'description of pain' as 'pounding heart in head' (85.9%).

Table 4.15. Frequency distribution of nominal test scores

Variable	**Category**	**% within Diagnosis**			
		Case Group		**Control Group**	
		Chronic CH (n = 45)	Episodic CH (n = 36)	Chronic migraine (n = 123)	Episodic migraine (n = 92)
Description	Pounding heart in the head	42.2	19.4	82.9	85.9
	Red hot poker in the eye	57.8	80.6	17.1	14.1
Restlessness	No	8.9	11.1	53.7	59.8
	Yes	91.1	88.9	46.3	40.2
Excruciating agony	No	8.9	11.1	53.7	59.8
	Yes	91.1	88.9	46.3	40.2
Headache at specific times	No	42.2	36.1	82.9	78.3
	Yes	57.8	63.9	17.1	21.7
Strictly unilateral pain	No	15.6	11.1	57.7	53.3
	Yes	84.4	88.9	42.3	46.7
Ipsilateral cranial autonomic symptoms	No	4.4	2.8	50.4	65.2
	Yes	95.6	97.2	49.6	34.8

Most patients diagnosed with chronic CH (91.1%) and episodic CH (88.9%) reported the presence of 'restlessness' during the attacks, whereas most patients diagnosed with chronic migraine (53.7%) and episodic migraine (59.8%) did not report 'restlessness'. Most patients diagnosed with chronic CH (57.8%) and episodic CH (63.9%) reported the presence of 'headaches at specific times', whereas most patients diagnosed with chronic migraine (82.9%) and episodic migraine (78.3%) reported the absence of 'headaches at specific times'.

Most patients diagnosed with chronic CH (84.4%) and episodic CH (88.9%) reported 'yes' for 'strictly unilateral pain', whereas most patients diagnosed with chronic migraine (57.7%) and episodic migraine (53.3%) reported 'no' for 'strictly unilateral pain'. Most patients diagnosed with chronic CH (95.6%) and episodic CH (97.2%) reported 'yes' for 'ipsilateral cranial autonomic symptoms', whereas most patients diagnosed with chronic migraine (50.4%) and episodic migraine (65.2%) reported 'no' for 'ipsilateral cranial autonomic symptoms'.

Figure 4.12 displays the frequency distributions of the total score for the 12 items in the screening tool, classified by diagnosis.

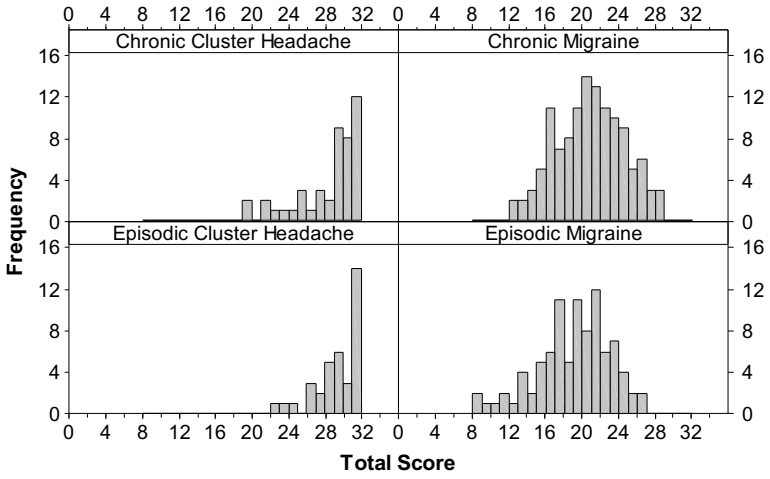


Figure 4.12. Frequency distribution of total score

Figure 4.13 compares the mean total score ± 95% CI of the patients classified by diagnosis. Patients with CH had a higher mean score (28.4; 95% CI 27,7; 29,1) compared to patients with migraine (19.5; 95% CI 19;20). Examination of the overlaps between the 95% CI indicated that the mean scores for the patients diagnosed with episodic (29.0; 95% CI 28.1;29.9) or chronic CH (28.1; 95% CI 27.0; 29.1) were higher than the scores for episodic (18.5; 95% CI 17.7;19.4) or chronic migraine (20.3; 95% CI 19.6; 21).

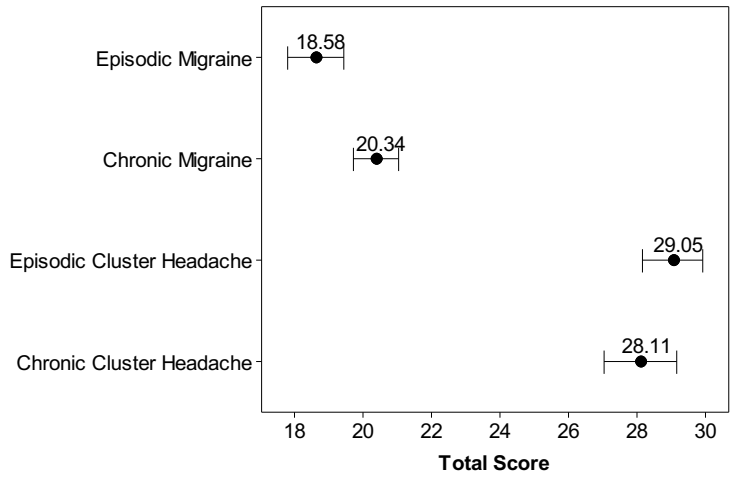
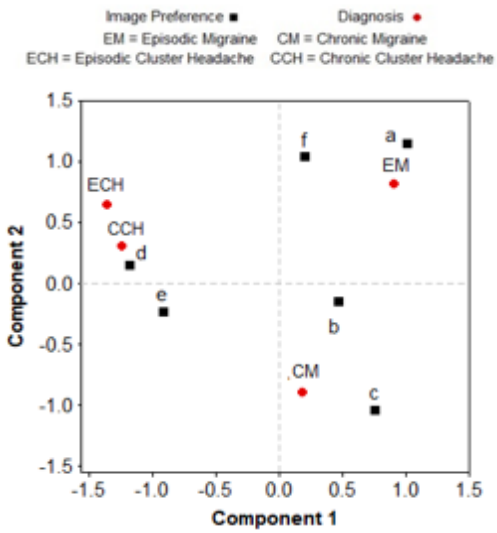


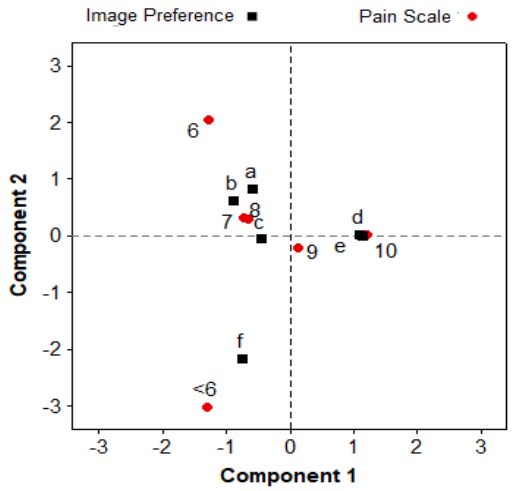
Figure 4.13 Mean total score ± 95% CI of patients classified by diagnosis

4.6.3.3 Correspondence analysis of the test scores

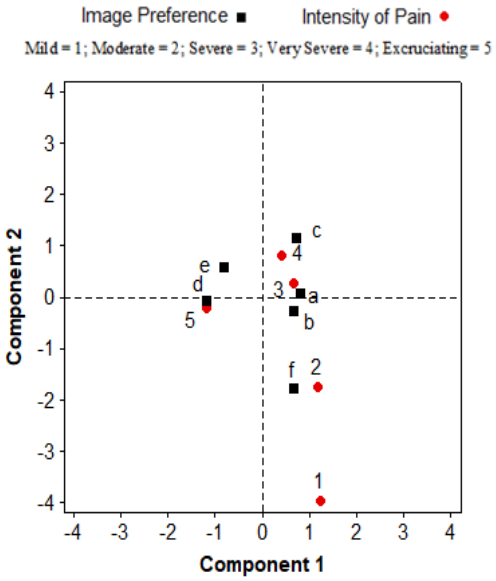
Correspondence analysis provides a graphical representation of the association between test items. Figure 4.14 displays the correspondence map between the six image preferences (a, b, c, d, or e) and other test items (restlessness, pain scale, excruciating agony, intensity of pain) according to four diagnoses (episodic or chronic migraine and episodic or chronic CH). Association between image preference and the four diagnoses was also determined (see Figure 4.14, Box 1). Component 1 and Component 2 axes in the correspondence maps arise from singular value decomposition allowing a projection of the multidimensional data (contingency table) in two dimensions while preserving correlation in data. Distance between points on the graph are proportional to the statistical independence of the variables which the points represent.



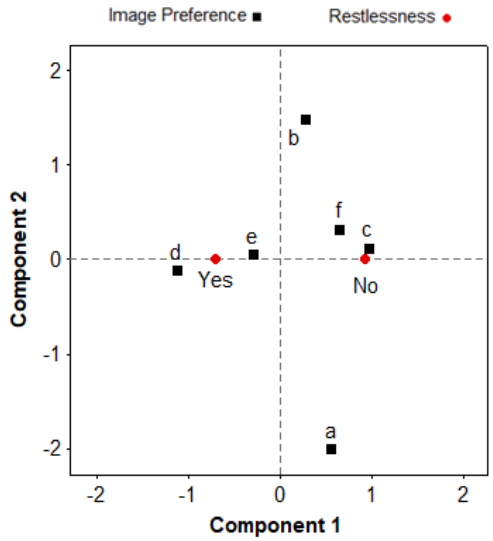
Box 1. Image preferences vs. Diagnosis



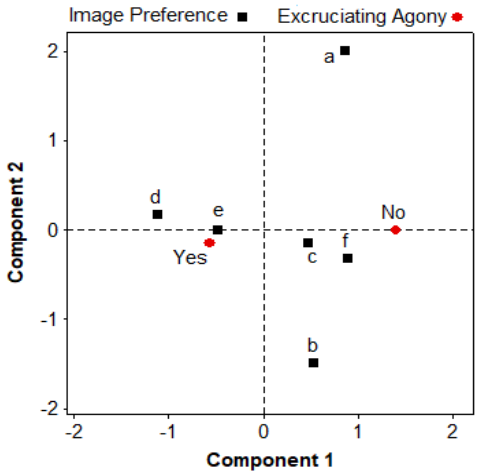
Box 2. Image Preference vs. Pain scale



Box 3. Image preference vs. Intensity



Box 4. Image Preferences vs. Restlessness



Box 5. Image preference vs. Excruciating agony

Figure 4.14. Correspondence maps between the image preference and other test items

Categories that were most closely associated with each other were represented by clusters of points located in near proximity. The cluster of points identified through correspondence analysis suggesting association between test items are presented in Table 4.16.

Table 4.16. Association between test items according to the correspondence maps

Test item	Cluster of points on the correspondence maps
Image preference vs. Diagnosis	Three clusters of points were identified. The cluster of points in the top right-hand quadrant reflected the close association of episodic migraine with 'image a' and 'image f'. The cluster of points in the bottom right-hand quadrant reflected the close association of chronic migraine with 'image b' and 'image c'. The cluster of points in the left-hand side of the map reflected the close association between 'images d' and 'image e' and episodic CH, and chronic CH (see Figure 4.14, Box 1).
Image preference vs. Pain scale	Three clusters of points were identified. The cluster of points in the top left-hand quadrant of the map reflected the close association of moderate pain scores 6, 7, and 8 with 'image a', 'image b', and 'image c'. The cluster of points in the bottom left-hand quadrant of the map reflected the close association of low pain scores < 6 with 'image f'. The cluster of points in the right-hand side of the map reflected the close association of the highest pain scores of 9 to 10 with 'images d' and 'image e' (see Figure 4.14, Box 2).
Image preference vs. Intensity of pain	Three clusters of points were identified. The cluster of points in the top left-hand quadrant of the map reflected the close association between score of 5 (excruciating) and 'images d' and 'image e'. The cluster of points in the top right-hand quadrant reflected the close association between scores 3 (severe) and 4 (very severe) with 'images a', 'image b', and 'image c'. The cluster of points in the bottom right-hand quadrant side of the map reflected the close association of the pain intensity scores 1 (mild) and 2 (moderate) with 'image f' (see Figure 4.14, Box 3).
Image preference vs. Restlessness	Two clusters of points were identified. The cluster of points in the left-hand side of the map reflected the close association of restlessness with 'images d' and 'image e'. The cluster of points in the top right-hand quadrant reflected the close association between the absence of restlessness and 'images f' and 'image c'. The points representing 'image a' and 'image b' were far located apart from the other points in the correspondence map. These results suggest that 'image a' and 'image b' are probably not associated with restlessness (see Figure 4.14, Box 4).
Image preference vs. Excruciating agony	Two clusters of points were identified. The cluster of points in the left-hand side of the map reflected the association of excruciating agony with 'images d' and 'image e'. The cluster of points at the centre on the right-hand side of the map reflected the close association between the absence of excruciating pain and 'images f' and 'image c'. The points representing 'image a' and 'image b' were far located apart from the other points in the correspondence map. These results suggest that 'images a' and 'image b' are probably not associated with excruciating agony (see Figure 4.14, Box 5).

4.6.3.4 Sensitivity and specificity statistics for items with dichotomous responses

The sensitivity and specificity statistics for the eight test items with binary responses are displayed in Tables 4.17-4.24. The results were interpreted assuming that a screening test should ideally exhibit a high level of sensitivity (to detect as many true-positives as possible). A high level of sensitivity was a beneficial outcome, because it meant that most of the patients were correctly diagnosed with CH whilst a moderately low specificity could be tolerated. However, a high false positive rate (i.e. a high probability of not identifying true-positives) was a detrimental outcome, because it meant that the patients were diagnosed with CH when, in fact, they should be diagnosed with migraine. The test with the highest sensitivity (100%) and lowest false positive rate (0.00 and 23%) was 'treated and untreated attack duration'. 'Ipsilateral cranial autonomic symptoms' had a high sensitivity (96%) but a moderate false positive rate (43%). 'Excruciating agony' also had a high sensitivity (93%) with a higher false positive rate (67%). 'Restlessness' was a symptom with high sensitivity (90%) and a moderate false positive rate (44%). 'Strictly unilateral pain' had a high specificity (86%) and a moderate false positive rate (44%). The 'description of the pain' had a lower level of sensitivity (68%) than the other symptoms, but it also had a lower false positive rate (16%). 'Headaches at specific times' had a low sensitivity (60%) but also with a low false positive rate (19%).

Table 4.17. Sensitivity and specificity statistics for 'description of pain'

Test item	CH present	CH absent	Total
Test positive (Red hot poker)	55	34	89
Test negative (Other)	26	181	207
Total	81	215	296
	Estimate	95% CI	
		Lower	Upper
Sensitivity %	68	58	78
Specificity %	84	79	89
FPR %	16	11	21
FNR %	33	22	38
PPV%	62	52	72
NPV %	87	83	92

Table 4.18. Sensitivity and specificity statistics for 'restlessness'

Test item	CH present	CH absent	Total
Test positive (Yes)	73	94	167
Test negative (No)	8	121	129
Total	81	215	296
	Estimate	95% CI	
		Lower	Upper
Sensitivity %	90	84	97
Specificity %	56	50	63
FPR %	44	37	50
FNR %	10	03	15
PPV %	44	36	51
NPV %	94	90	98

Table 4.19. Sensitivity and specificity statistics for 'excruciating agony'

Test item	CH present	CH absent	Total
Test positive (Yes)	75	143	218
Test negative (No)	6	72	78
Total	81	215	296
	Estimate	95% CI	
		Lower	Upper
Sensitivity %	93	87	98
Specificity %	33	27	40
FPR %	67	60	73
FNR %	07	02	13
PPV %	34	28	41
NPV %	92	86	98

Table 4.20. Sensitivity and specificity statistics for 'headache at specific times'

Test item	CH present	CH absent	Total
Test positive (Yes)	49	41	90
Test negative (No)	32	174	206
Total	81	215	296
	Estimate	95% CI	
		Lower	Upper
Sensitivity %	60	50	71
Specificity %	81	76	86
FPR %	19	14	24
FNR %	40	29	46
PPV %	54	44	65
NPV %	84	80	89

Table 4.21. Sensitivity and specificity statistics for 'strictly unilateral pain'

Test item	CH present	CH absent	Total
Test positive (Yes)	70	95	165
Test negative (No)	11	120	131
Total	81	215	296
	Estimate	95% CI	
		Lower	Upper
Sensitivity %	86	79	94
Specificity %	56	49	62
FPR %	44	38	51
FNR	14	06	19
PPV %	42	35	50
NPV%	92	87	96

Table 4.22. Sensitivity and specificity statistics for 'ipsilateral cranial autonomic symptoms'

Test item	CH present	CH absent	Total
Test positive (Yes)	78	93	171
Test negative (No)	3	122	125
Total	81	215	296
	Estimate	95% CI	
		Lower	Upper
Sensitivity %	96	92	100
Specificity %	57	50	63
FPR %	43	37	50
FNR %	4	0.0	7.0
PPV %	46	38	53
NPV %	98	95	100

Table 4.23. Sensitivity and specificity statistics for 'untreated attack duration'

Test item	CH present	CH absent	Total
Test positive (≤3h)	81	0	81
Test negative (>3h)	0	215	215
Total	81	215	296
	Estimate	95% CI	
		Lower	Upper
Sensitivity %	100	100	100
Specificity %	100	100	1.00
FPR %	0.0	0.0	0.0
FNR %	0.0	0.0	0.0
PPV %	100	100	100
NPV %	100	100	100

Table 4.24. 'Sensitivity and specificity statistics for 'treated attack duration

Test item	CH present	CH absent	Total
Test positive (≤ 3h)	81	50	131
Test negative (> 3h)	0	165	165
Total	81	215	296
	Estimate	95% CI	
		Lower	Upper
Sensitivity %	100	100	100
Specificity %	77	71	82
FPR %	23	18	29
FNR %	0.0	0.0	0.0
PPV %	62	54	70
NPV %	100	100	100

The sensitivity and specificity statistics for the eight test items with dichotomous responses are summarised in Table 4.25. The test items with the highest sensitivity included 'treated and untreated attack duration' (100%), followed by the presence of 'ipsilateral cranial autonomic symptoms' (96%), attacks described as 'excruciating agony' (93%), and the presence of 'restlessness' (90%). The highest specificity was recorded for 'untreated attack duration' (100%), 'description of pain' (84%), and 'attacks at specific times' (81%). All eight test items had a high NPV (>80%) in detecting CH. After the 'treated and untreated attack duration', the 'description of pain' had the highest PPV (62%). The highest NPV were recorded for the 'treated and untreated attack duration' (100%) and the presence of 'ipsilateral cranial autonomic symptoms' (98%).

Table 4.25. Summary of sensitivity and specificity statistics for the eight items with binary responses

Test item	Sensitivity % (CI)	Specificity % (CI)	PPV % (CI)	NPV % (CI)	FPR % (CI)	FNR % (CI)
Description of pain	68 (58;78)	84 (79;89)	62 (52;72)	87 (83;92)	16 (11;21)	32 (22;38)
Presence of restlessness	90 (84;97)	56 (50;63)	44 (36;51)	94 (90;98)	44 (37;50)	10 (3;15)
Excruciating agony	93 (87;98)	33 (27;40)	34 (28;41)	92 (86;98)	67 (60;73)	7 (2;13)
Attacks at specific times	60 (50;71)	81 (76;86)	54 (44;65)	84 (80;89)	19 (14;24)	40 (29;46)
Strictly unilateral pain	86 (79;94)	56 (49;62)	42 (35;50)	92 (87;96)	44 (38;51)	14 (6;19)
Ipsilateral cranial autonomic symptoms	96 (92;100)	57 (50;63)	46 (38;53)	98 (95;100)	43 (37;50)	4 (0.0;7)
Treated attack duration ≤3h	100 (100;100)	77 (71;82)	62 (54;70)	100 (100;100)	23 (18;29)	0 (0.0;0.0)
Untreated attack duration ≤3h	100 (100;100)	100 (100;100)	100 (100;100)	100 (100;100)	0 (0.0;0.0)	0 (0.0;0.0)

Abbreviations: PPV: positive predictive value; NPV: negative predictive value, FPR: false positive rate; FNR: false negative rate

4.6.3.5 Determining the overall performance of the screening tool

In this section, I first present the performance of the ordinal test items such as 'image preference', 'pain intensity', 'pain scale' and 'nature of pain'. I continue with a section on the results of the total test score in differentiating between CH and migraine and I conclude with the gender segregated analysis and analysis with class balancing.

ROC analysis for whole data set

The ROC analysis was performed for the ordinal test items and the total test score. Figure 4.15 illustrates the ROC curves for 'image preference', 'pain scale', 'intensity of pain', 'nature of pain', and 'total score'. The areas under all of the ROC curves were >0.5 ($p < 0.001$), implying the specified variables significantly distinguished between patients with CH, and patients with migraine. None of the tests were worthless. The ROC curves also permitted the identification of cut-off test scores that best distinguished between patients with CH and patients with migraine. The cut-off scores are identified in Table 4.26. Based on the area under the curve (AUC), the most accurate test was the 'total score' (0.955 = excellent); followed in order of magnitude by 'intensity of pain' (0.841 = good); 'pain scale' (0.799 = fair); 'image preference' (0.723 = fair); and 'nature of pain' (0.702 = fair). The 'total score' for the 12 items appeared to provide a more accurate method to distinguish between patients with CH and patients with migraine than the separate scores for 'image preference', 'pain scale', 'intensity of pain' and 'nature of pain'. When the images were removed from the analysis, the 'total score' proved to be a more accurate test (sensitivity 92.6%, specificity 93.9%) compared to the 'total score' of the 12 items (sensitivity 86.4%, specificity 92.0%).

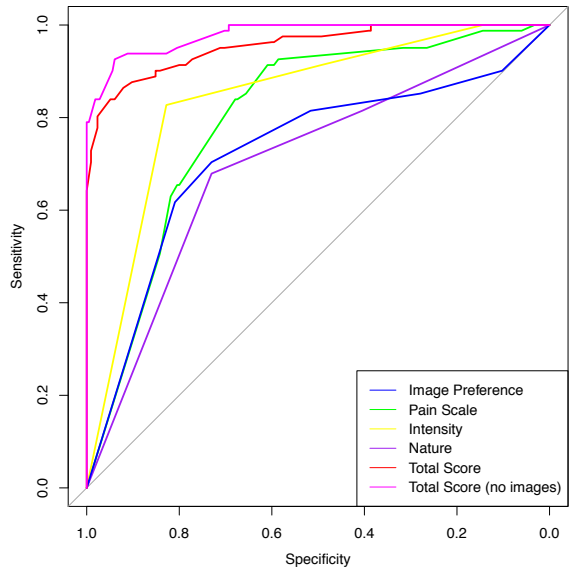


Figure 4.15. ROC curves for whole data set

Note: AUC: Area under the curve; AUC Total score=0.955; Total score (no images) =0.979; AUC Intensity=0.841; AUC Pain scale=0.799; AUC Image preference=0.723; AUC Nature of pain=0.702; AUC is significantly greater than 0.5 ($p < .001$)

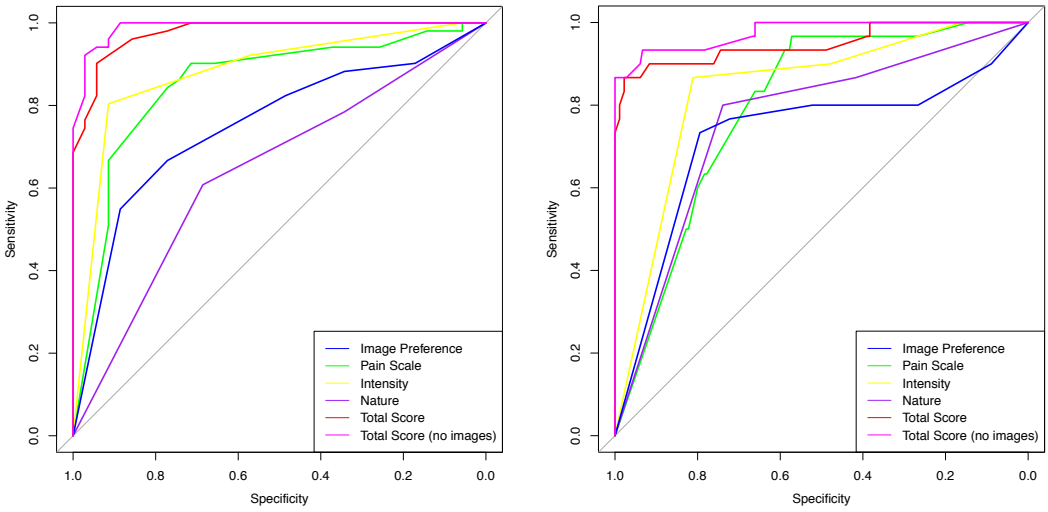
Table 4.26. Cut-off points on the ROC curves for whole data set

Test item	Cut-off	Sensitivity (%)	Specificity (%)
Nature of pain	3 (Stabbing/Burning)	67.9	73.0
Image preference	5 (Image e)	70.3	73.0
Intensity of pain	5 (Excruciating)	82.7	82.7
Pain scale	9 (out of 10)	83.9	67.9
Total score	**25 (out of 32)**	**86.4**	**92.0**
Total score (without images)	**20.5 (out of 32)**	**92.6**	**93.9**

ROC analysis according to gender

Gender segregated analysis informed on the differences in the clinical characteristics between males and females. Figure 4.16 shows the ROC curves according to gender. The cut-off points on the ROC curves are presented in Table 4.27. Similar to the analysis including the whole data set, the 'total score' is the most precise test in differentiating CH from migraine according to the gender analysis. The 'total score' >23 (out of 32) had a high performance (sensitivity 90.1%, specificity 94.2%) for males with CH. The 'total score' >25/32 has a slightly lower specificity for females with CH (sensitivity 90.0%, specificity 91.6%). Without the images, the 'total score' has a slightly better performance than the 'total score' of the 12-items for both male and female groups. The intensity of pain 'excruciating' has a higher specificity for males

with CH (91.4%) than females (81.1%). The image preference has a slightly higher performance for females (sensitivity 73.3%, specificity 79.4%) than males with CH (sensitivity 66.6%, specificity 77.1%). Overall, the gender segregated analysis did not reveal significant differences between males and females.



ROC curve for the male group ROC curve for the female group

Figure 4.16. ROC curves according to gender

Note: AUC male group: AUC Total score=0.977; AUC Total score (no images)=0.979; AUC Intensity=0.881; AUC Pain scale=0.852; AUC Image preference=0.751; AUC Nature of pain=0.640;
AUC female group: AUC Total score=0.948; AUC Total score (no images)=0.975; AUC Intensity=0.838; AUC Pain scale=0.795; AUC Image preference=0.726; AUC Nature of pain=0.761;. Area under ROC curve is significantly greater than 0.5 ($p < .001$)

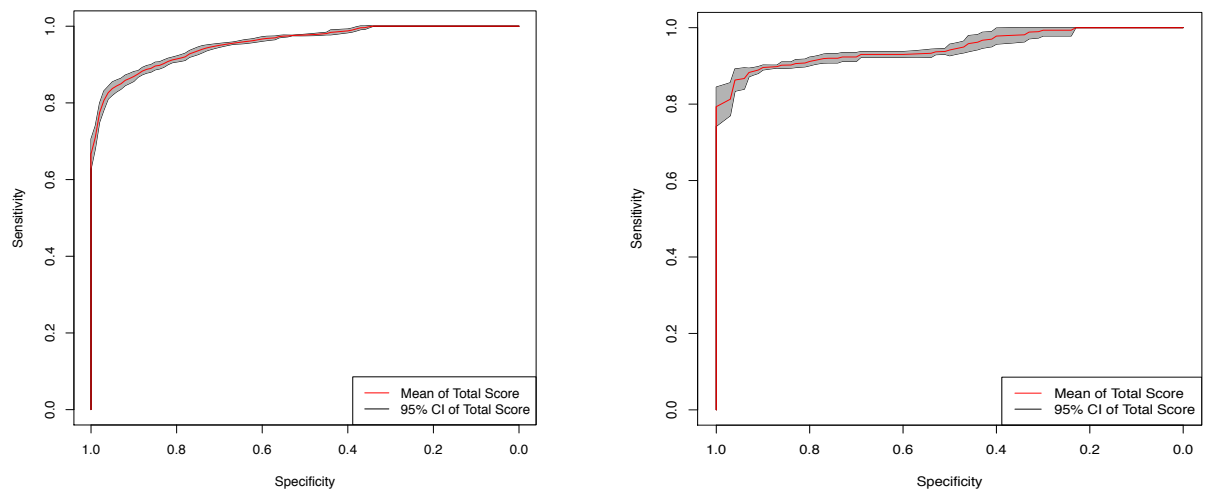
Table 4.27. ROC cut-off points for the male and female groups

Statistics according to gender		**Nature of pain**	**Image preference**	**Pain scale**	**Intensity of pain**	**Total score**	**Total score (without images)**
Cut-off	Male	3	5	9	5	23.6/32	20/32
	Female	3	6	9	5	25.0/32	20.5/32
Sensitivity (%)	Male	60.7	66.6	84.3	80.3	90.1	94.1
	Female	80.0	73.3	83.3	86.6	90.0	93.3
Specificity (%)	Male	68.5	77.1	77.1	91.4	94.2	94.2
	Female	73.8	79.4	66.1	81.1	91.6	93.3

Note: Cut-off points: Nature of pain 3=Stabbing/burning; Image preference 5='Image e' (excruciating); Image preference 6= Image 'd' (excruciating); Intensity of pain 5= Excruciating; Pain scale = 9 (out of 10)

ROC analysis with class balancing

To evaluate the influence of the unbalanced classes on the statistical analysis on Figure 4.17, I performed ROC analysis with class balancing. The data set is unbalanced in two ways: due to more females than males in the data set and more occurrences of migraine than CH. Figure 4.17 shows the mean ROC curve and associated 95% CI of the 'total score' for the whole data set and for the female group, respectively, after class balancing. Balancing was performed by gathering 10 random under-samplings of the occurrences of migraine from the complete data set including both males and females. ROC curve for each realization of the random under-sampling were averaged to obtain the presented ROC curves. Class balancing does not alter the characteristics of the ROC curve. Hence, unbalanced classes do not affect the accuracy of the results.



Whole data set balanced for the occurrences of migraine

Whole data set with gender balancing

Figure 4.17. ROC curve of the total score after class balancing

4.7 Discussion

In this section, I first discuss the profile of patients with migraine and CH in this study. I continue with a section on the clinical characteristics that best differentiate CH from migraine. I further address the usefulness of the screening tool in detecting CH and the role of images depicting headache pain. I conclude with a section of the study's strengths and limitations.

4.7.1 Profile of patients with headache

This study included males and females with a diagnosis of episodic and chronic CH, episodic and chronic migraine. The male:female ratio in the CH group is 1.7:1, in line with previous data (4, 16, 17). There is increasing evidence of better recognition of CH in females, shifting the gender ratio from 5-6:1 (12, 13) or 8-9:1(14, 15) to an estimated 2-3:1(4, 16, 17). Decline in the gender ratio suggests that CH is not as male dominated as once thought (293). Ten to 15% of patients with CH have chronic CH (9). The percentage of patients with chronic CH in this study is higher (36 patients with episodic CH; 45 patients with chronic CH) which reflects what is seen in a tertiary headache centre where chronic patients are overrepresented (16). Migraine disproportionally affects females, also reflected in this study (female:male 5.1:1) (294). Patients with episodic migraine in this study have a lower mean age compared to other groups of patients. This is in keeping with previous reports that showed a similar mean age (295). As episodic migraine can progress into chronic migraine (296), the mean age of patients with chronic migraine tends to be higher (297). Previous research reports a rate of progression of 2.5% per year (298). The higher prevalence of chronic migraine at a headache clinic (299) compared to the total migraine population (7.68%) (300) is also reflected in this study (57.2%).

4.7.2 Clinical indicators of CH versus migraine

The current literature reports key clinical differences between CH and migraine including duration of pain, intensity of pain, restlessness behaviour during attacks (1), and presence of ipsilateral cranial autonomic symptoms (169). The current study assessed if these key clinical characteristics could differentiate between CH and migraine patients recruited from a tertiary headache centre.

CH is often described in the literature as the 'most severe pain known to man' of excruciating quality (7, 289, 301, 302). Although such pain descriptor is not usually attributed to migraine (303), it proved to have a low specificity in detecting CH (33%) in this study. Furthermore, both the pilot and the larger-scale study showed that patients with migraine can regard their pain as 'excruciating agony', a pain descriptor typically associated with CH (7, 304). This is in line with previous research conducted by Torelli et al. that reported low specificity (34%) for the descriptor '*excruciating pain'* in detecting CH (257). This descriptor of pain does not seem to be reliable in differentiating between CH and migraine. Moreover, discrepancy in pain reporting was found among patients with migraine. Almost half of the

patients with migraine (43%) experienced 'excruciating agony' but less patients rated their pain as 'excruciating' (16%) on the intensity scale from mild to excruciating. Among the CH group, the intensity of pain (from mild to excruciating) is a more accurate test in detecting CH than attacks described as 'excruciating agony'. This highlights the importance of question phrasing that could influence the pain information provided, as shown by McDonald in a study on patients with osteoarthritis (305). Furthermore, the findings of the pilot and larger-scale study are not all consistent. 'Excruciating' intensity of pain was chosen by more patients with migraine in the pilot study compared to the larger-scale study (46% versus 16.4%). This inconsistency in intensity reporting could be due to the presence of more patients with chronic migraine in the pilot study (93% versus 57%), resulting in higher disease disability which affects how pain is recounted (298). The data analysis showed that the pain described as a 'red hot poker in the eye' had a higher specificity than 'excruciating agony' (84% versus 33%) in detecting CH. In a clinical setting, the pain described as 'red hot poker in the eye' could be more indicative of CH than migraine.

According to data analysis, the descriptor of pain 'excruciating agony' and the intensity of pain (mild to excruciating) are not good discriminators between CH and migraine. This could be secondary to multiple biases that characterise pain reporting. Recall of pain intensity is exaggerated and also chronic pain itself is associated with overestimation of pain intensity, as shown by Jamison in his study on chronic pain patients (306). The same study found that cervical and low back pain patients were found to be more accurate than headache patients in remembering their pain but the reason is unknown (306). Also, associated psychiatric co-morbidities could have an influence on how pain is reported (307). The self-report of physical pain can also be subjected to recollection bias (308, 309), as shown by recent research whereby patients with CH overestimated the severity of retrospective attacks compared to the attacks recorded prospectively (310).

Other clinical features that could differentiate between CH and migraine captured in this study were the duration of pain, the presence of restlessness behaviour and ipsilateral cranial autonomic symptoms accompanying the attacks. The current study showed that the untreated attack duration (≤ three hours) is the best clinical feature to distinguish between CH and migraine which is in line previous data (257, 258, 262). Nevertheless, these findings are a limitation of strictly applying the ICHD-3 criteria where CH patients with attacks longer than three hours are excluded from the research studies (1, 311). CH attacks are typically associated with restlessness and prominent ipsilateral cranial autonomic symptoms (1). These clinical characteristics had high sensitivity (>90%) but low specificity (<60%) in detecting CH which

meant they were present in many patients with migraine. Previous studies report variable results for the presence of restlessness during CH attacks (80% (312), 67.9% (224), 51% (313)). This could be due to differences in question phrasing although the questionnaires used for data collection were not available in these studies (224, 312, 313). Previous research found higher sensitivity for the presence of restlessness in patients with chronic CH (sensitivity 100%, specificity 90%) than episodic CH (sensitivity 82%, specificity 92%) but the reason is unknown (257). In the current study, the presence of ipsilateral cranial autonomic symptoms were reported in 96% of patients with CH and 42% of patients with migraine, similar to existing data (169). According to previous reports, cranial autonomic symptoms were present in 56% of patients with migraine but were less severe, usually bilateral and inconsistent from one attack to the other (169). In contrast, the cranial autonomic symptoms reported in 94% of patients with CH were severe, unilateral and consistently present from one attack to the other (169). The severity and consistency of cranial autonomic symptoms were not captured in this doctoral research.

4.7.3 The screening tool's role in detecting CH

In this study, a self-administered questionnaire was developed to rapidly identify patients with CH and decrease the common misdiagnosis of migraine. The main objectives of this study were to determine the overall performance of the screening tool and the performance of individual test items. The usefulness of images depicting headache pain in detecting CH was also assessed. This study showed many overlapping features between CH and migraine which could account for the diagnostic delays and misdiagnosis. There is no single test item that can differentiate between the two conditions.

Pictures of pain have been shown to be an invaluable tool in the study of pain and offers insight into the neural networks involved in pain perception (314). The diagnostic process is usually focused on the sensory experience of pain while the emotional aspects are neglected (315). Therefore, images depicting pain could be considered a more complex representation of the pain experience. Images depicting different pain severities that were included in the screening tool are shown in Figure 4.18.

Figure 4.18. Images depicting different pain severities

'Image a' depicts moderate pain; 'Image b'- severe pain; 'Image c'- moderate/severe pain; 'Image d' and 'Image e' - excruciating pain; 'Image f'- mild pain (rating according to healthy participants, see section 4.6.1.1)

Data analysis suggests that images with the highest intensity ('image d', 'image 'e') (39) are more likely to discriminate between CH and migraine (sensitivity 70%, specificity 73%) compared to other images. Furthermore, the findings emphasise that 'image d' is more illustrative of CH attacks (61%) than migraine attacks (18%), probably due to the higher intensity portrayed by this image (39). When comparing the results from the pilot versus larger-scale study, a difference in image preference emerged among patients with migraine. 'Image d' was preferred by 52% of migraine patients in the pilot study compared to 18% in the larger-scale study. Similarly, a higher pain intensity was recorded among patients with chronic migraine in the pilot study compared to the larger-scale study. As discussed in section 4.7.2., a higher disease burden among patients with chronic migraine in the pilot study could have influenced pain reporting (307). As a consequence, this could have led to reporting a higher pain intensity and selecting an image with higher severity. This is also reflected in the image preference of patients with chronic versus episodic migraine. Patients with chronic migraine selected images with higher severities ('image b', 'image c') compared to patients with episodic migraine ('image a'; 'image f'). This discrepancy in image preference is not present

among episodic and chronic CH patients, which could suggest similar disease disability among these two groups.

There was consensus among all groups of participants (healthy participants, patients with CH, patients with migraine) on the pain intensity depicted by each image (e.g. 'image d' and 'image e' - excruciating pain). This could suggest a similar perception of the pain intensity depicted by images among all groups. The presence of restlessness during the attacks and attacks perceived as an 'excruciating agony' were associated with selecting images with the highest severity ('image d', 'image e'). Therefore, images depicting headache pain could give insight into other symptoms accompanying the headache attacks. However, the images depicting headache pain do not clearly discriminate between CH and migraine. This could be due to the fact that images mainly seem to evoke different pain intensities which do not clearly differentiate between the two conditions. Other images with different artistic characteristics could be tested in future work. Apart from the headache intensity, images depicting headache pain might evoke certain emotions associated with the pain experience (315). This emotional aspect of pain was not explored in this study and could be assessed in future qualitative research.

The total screening tool score proved to be the best test in differentiating between CH and migraine. A total screening tool score with a cut-off > 25/32 was highly sensitive (86.4%) and specific (92%) in detecting CH. Furthermore, patients with CH had a higher mean score compared to patients with migraine (28.4 versus 19.5). The tool in this study was developed for the screening of CH and requires validation in other clinical settings including primary care. If applied in primary care, higher questionnaire scores (>25/32) could trigger a referral to secondary care for confirmation of diagnosis. This way, patients with CH can be detected when otherwise they may have been misdiagnosed.

4.7.4 Strengths and limitations

The strength of this study is that it is the first of its kind to use visual aids to assess and facilitate the diagnosis of primary headaches. A methodological advantage of this study is the type of screening tool used. This study developed a short questionnaire which decreases the chance of hasty or slapdash responses (316). Furthermore, the headache experience was captured in four different ways: through images depicting headache pain, descriptors of pain, key questions that could differentiate between CH and migraine, and a visual analogue pain scale. Other strength of this study is that a preliminary version of the screening tool was tested in a pilot study with

a smaller sample size and the questionnaire was refined based on patients' feedback. The new questionnaire was tested in a larger-scale study. The study included an adequate sample size, comprised of a control group of patients with migraine, the most common misdiagnosis of CH (317).

This study was subjected to limitations. The patients were recruited from a tertiary headache centre after they received a diagnosis of CH or migraine, which may have resulted in selection bias of the enrolled patients. The patient sample is drawn from a setting in a tertiary headache clinic, and the results may therefore not be representative of CH in the general population since the specialist clinics see the most disabled patients. In this study, and also in other samples of patients attending headache units, patients with chronic headaches were over-represented (318). The screening tool should be further validated in primary care settings and population-based studies. This study was based on the ICHD-3b criteria which included the recently deleted symptom (fullness in the ear) from the ICHD-3 criteria and extending the maximum remission periods of chronic CH to up to three months (1). Although, there was no difference in reporting ipsilateral ear fullness between patients who received a diagnosis of CH and patients who did not (319), the screening tool needs to be evaluated with the current ICHD-3 criteria. This study did not include the sign miosis, contained in both ICHD-3b and ICHD-3 criteria. Patients rarely notice this sign as they do not look in the mirror during the attacks (57). Similar was reported regarding patients with migraine with associated cranial autonomic symptoms (320). Recall bias, a limitation characteristic to all survey studies, may have affected the findings (309). Patients might have had problems remembering the details regarding their headache attacks. The patients in this study completed the questionnaire unaided and there was no flexibility to rephrase the questions or to introduce examples to make sure the questions were correctly understood. Retest reliability was not performed for this study which it should be evaluated in future research.

4.8 Conclusions

CH is a severe primary headache often misdiagnosed in primary care. Although CH and migraine share similar clinical features which might contribute to misdiagnosis, there are key differences in their clinical characteristics and management. In this study, I developed a novel 12-item screening tool to aid the diagnosis of CH. Six images depicting pain, verbal descriptors of pain, key questions that could differentiate between CH and migraine, and a visual analogue pain scale, comprised the screening tool. The screening tool was tested on patients with CH

and migraine (control group). The images tested on healthy participants showed different pain severities. The screening tool was refined based on patients' feedback in a pilot study. The total screening tool score with a cut-off > 25/32 was highly sensitive in differentiating CH from migraine (sensitivity of 86.4% and specificity of 92%). Patients with CH had a higher mean score compared to patients with migraine (28.4 versus 19.5). The images depicting headache pain do not clearly differentiate between CH and migraine. A newly developed screening tool could aid the diagnosis of CH and avoid the common misdiagnosis of migraine.

CHAPTER 5. EXPERIENCES, UNDERSTANDINGS AND PERCEPTIONS ON CLUSTER HEADACHE DIAGNOSIS: A QUALITATIVE STUDY

5.1 Introduction

In this chapter I present my analysis of a qualitative dataset around the diagnostic journey of patients with CH. I first introduce the theoretical framework, drawing on concepts from the sociology of health and illness. I map out the few existing sociological studies on headache, the sociology of diagnosis, and the sociological concept 'biographical disruption' in chronic illness. I continue by proposing the biopsychosocial model as an alternative approach to the biomedical model, the approach still dominant in contemporary medicine. This is followed by a methods section outlining the CHIPS study: a qualitative semi-structured interview study with participants with CH, GPs and neurologists. I was member of the CHIPS research team and I conducted the data analysis which focused on the diagnostic journey of participants with CH from the perspective of the three main key stakeholder groups: participants with CH, GPs and neurologists.

5.2 Qualitative and sociological research on primary headaches

In the last decades qualitative research has increasingly become acknowledged and embedded in health research (321, 322). Health researchers now recognise the ways in which qualitative methodologies can contribute to our understanding of clinical issues (e.g. patients' uptake of medical recommendations) and how qualitative research can answer questions about the organisation and culture of those providing healthcare and those at the receiving end. Pope and Mays (1995) aptly refer to the contribution of qualitative research as 'reaching the parts other methods cannot reach' (323). Indicative of the increased recognition of qualitative health research is the 2008 series in the *British Medical Journal* within which its readership was introduced to the major qualitative approaches such as grounded theory, mixed methods, action research (324), ethnography (325) and discourse analysis (326).

Qualitative research has not yet been fully adopted in the field of headache studies. It is only in recent years that headache disorders have been studied using qualitative methodologies.

Although qualitative data on primary headaches such as migraine (327), TTH (328) and medication overuse headache (329) are better represented in the literature, qualitative methods were applied in solely two CH studies thus far (330, 331). In the first qualitative study on CH, Palacios-Cena et al. explored the experiences of males living with CH (330). They showed that men with CH live in fear and uncertainty due to intensity of the attacks, scepticism from social and workplace environments and lack of awareness among clinicians (330). The second qualitative study, conducted by Andersson et al. explored the self-treatment of CH and migraine and identified a desperate need for effective treatments, the role of the forum-finding alternative treatments and community support (331).

In most qualitative research studies, a sociologist and/or qualitative health service researcher is part of the research team and introduces social scientific conceptual frameworks to interpret the qualitative data. To date, social scientists have not focused their attention on primary headaches. A notable exception is the work by sociologist Kempner. Most of her work revolves around the gender dimension of primary headaches, with studies on migraine (294, 332) and one on CH (293). In her book, 'Not Tonight: Migraine and the Politics of Gender and Health', Kempner examines migraine-associated stigma affecting the identity of the person with migraine and impairing the ability to seek and receive care (294). Kempner uses migraine and CH as comparative cases drawn around stereotypes of gender among clinicians. Migraine is characterised by passive retreat in a quiet place, seen as a feminine trait while CH is characterised by restlessness and aggressive behaviour regarded as masculine features (332). As Kempner concludes, there is increasing evidence that CH is not as male dominated as once thought and a better recognition in women could avoid misdiagnosis (293).

5.3 Relevant theoretical concepts from medical sociology

Key concepts from the sociology of health and illness are important in interpreting qualitative data around the diagnostic process and patients' perceptions and experiences of their diagnostic journeys. I address here sociological concepts which are relevant to the topic of my doctoral research, such as 'the doctor-patient relationship' and 'biographical disruption'. I start with the relatively new sociology of diagnosis and conclude the section by proposing the biopsychosocial model as an alternative to the biomedical approach.

5.3.1 Sociology of diagnosis

Sociology of diagnosis is a relatively new field in sociology, first conceptualised by sociologist Brown in 1990 (333). Sociologist Jutel has focussed most of the work in building on that concept and further refining the sociology of diagnosis (334). To date, more attention is focused on conditions such as diabetes (335) or cancer (336), while headache disorders are neglected despite their high prevalence and impact (337). In Jutel's review on the sociology of diagnosis, she describes diagnosis as a label that legitimises the illness, the individual who is sick finds herself/himself treated rather than blamed (334). Receiving a diagnosis of certain diseases and its social influence are discussed in her book, 'Putting a name to it: diagnosis in the contemporary society', that addresses the social impact of receiving a particular diagnosis and also the lay-professional relationship (338). Jutel debates the importance of the legitimacy of disease, which is partly received and symbolised through the diagnosis. A disease diagnosis impacts on how others react towards and view the sufferer and the influence on identity and self-perception of the sufferer (338). Jutel also argues that the diagnosis has administrative purposes as it enables access to previously unauthorised privileges such as medication, disability payments, sick leave and access to support groups (338). In her work about disclosure and the power of diagnosis, Jutel debates that the diagnosis pronouncement is almost as important as the disease itself (339).

'Diagnostic limbo' is another concept from medical social sciences, used to describe the lack of diagnosis or misdiagnosis. In her qualitative study on Parkinson's disease, Peek outlines the challenges with diagnosis often stuck in a limbo (340). Nettleton identified in her interview study with neurology outpatients with medically unexplained symptoms, difficulties of living with uncertainty and dealing with legitimacy (341). As evidenced by medical sociologists, the process of diagnosis has multiple psychosocial implications for the individual. The process of diagnosis might finalise with different outcomes for the sufferer. On the basis of her extensive research, Jutel builds further on Blaxter's process of diagnosis and defines it as *'conveyed'* (too passive, like a property transaction), '*awarded*' (when having a label opens doors), '*branded'* (when it is a stigmatising diagnosis), '*applied'* (like trying on a new lipstick) or '*disclosed'* (when the complexity and severity of the condition requires discretion) (338). Jutel argues that the absence of diagnosis has implications for the doctor-patient relationship and challenges the authority of the medical professional (338). The next section addresses the doctor-patient relationship in the process of diagnosis.

5.3.2 The doctor- patient relationship

The social encounter between doctor and patient has received considerable attention in the sociological literature. The ways doctors and patients interact has been of interest for social theorists. Sociologist Morgan describes different models of the doctor-patient relationship: (1) a paternalistic relationship (high physician control and low patient control); (2) a relationship of mutuality (active involvement of patients as more equal partners in the consultation); (3) a consumerist relationship (patient has an active role and the doctor adops a passive role; e.g. second opinion, sick note); (4) a relationship of default (the consultation lacks a clear direction) (342). The standardization of medical practice, relying on 'evidence-based medicine' ignores the variation in patients' preferences and characteristics, as argued by sociologist Goold (343). This influenced the doctor-patient relationship, which transitioned from a patternalistic model to a patient-centred approach, in sociologist Kaba's view (344).

The pursuit of diagnosis often brings the patient and doctor together. Psychoanalyst Balint defines this pursuit as the most pressing problem for the patient: 'the request for the name of the illness, for diagnosis' (345). The implications of clinical uncertainty around diagnosis could negatively influence the doctor-patient relationship, as argued by sociologist Calnan (346). In his study, the '*worst patients',* as he puts it, were those who questioned physician's judgement, usually patients with chronic illness who required frequent medical encounters (346). Sociologist Lupton explored the way lay people feel about medicine and the medical profession in an interview study with lay participants from a wide range of different backgrounds (347). Lupton's findings are that lay people may pursue the 'consumerist' or 'passive patient' roles depending on the context (347). Furthermore, lay individuals are ready to challenge, discuss, contest their doctor or to seek advice outside the doctor-patient relationship (347). Today, digital self-diagnosis challenges the authority of the health professional, who traditionally makes the diagnosis (348). The availability of medical knowledge reduces the power of the clinician and transforms the patient into an '*informed consumer'*, as Jutel puts it (338). In her work about digitizing diagnosis, Jutel concluded that diagnostic tools such apps and websites potentially reconfigure disease concepts and doctor-patient relations but also raise the risk of presenting inaccurate information (348). Although the access to digital information can have its drawbacks, it was perceived to have a positive influence on the doctor-patient relationship in a study that explored oncologists' perceptions on the use of internet of patients with prostate cancer (349). Seeking biomedical information from the internet was seen to increase patients' motivation to be involved in the decision

making, increasing the understanding in the treatment options and possible adverse events (349).

Other sociological concept of relevance to my work is that of 'biographical disruption' in the context of chronic illness.

5.3.3 Chronic illness and the notion of 'biographical disruption'

The concept of biographical disruption, introduced by Bury in the early 1980s (350), describes the severe impact of chronic illness on individual's daily life and sense of identity (351, 352). Saunders examined the concept in his investigation of how the identity of young adults with inflammatory bowel disease has changed (351). Profound biographical disruption was described in one of the patients with ulcerative colitis, who experienced weight gain as a side effect of anti-inflammatory steroid medication: '*my self-esteem had just hit rock bottom'* (351). Another patient failed to achieve important milestones such as obtaining a postgraduate degree as a result of significant disruption caused by Crohn's disease (351). According to Saunders, recurrent episodes of biographical disruption can occur when illnesses are characterised by relapses separated by periods of remissions (351). The individual is forced to reformulate the concept of self in the light of the illness, inexistent from the normality of the previously disease-free biography (351). Saunders suggests that biographical disruption is more likely to occur in young individuals as the illness is often unexpected (351). The strong link between chronic illness and biographical disruption is reinforced in Wilson's qualitative study on HIV infection and motherhood (352). He suggests a fundamental reformulation of participants' identities due to mothers' need to survive and protect their children (352). Blos described young adulthood as a '*decisive turning point in developing self-identity'* (353) which can suffer substantial biographic change in the face of chronic and unpredictable conditions (354). In a qualitative study with chronic knee pain patients, Morden found that individuals with intermittent conditions experience fear of '*future disruptions'* to their life produced by the recurrence of disease (355). According to Reeve et al.'s interview study on patients with terminal cancer, worries about the future are disruptive in themselves (356). Some patients in this study experienced 'biographical fracture', defined by the researchers as a significant biographical disruption associated with profound distress and the need for external support (356).

5.3.4 Biopsychosocial model of illness

The biopsychosocial model, first introduced by Engel in the late 1970s, emerged from the dissatisfaction with the dominant biomedical model (357). Engel outlined that the biomedical model left '*no room within its framework for the social, psychological and behavioural dimensions of illness'* (357). Wade and Halligan argue that it is now generally accepted that diseases are the result of the interaction between biological, psychological and social factors and should be treated through a biopsychosocial approach (358). In 2002, the World Health Organisation published the International Classification of Functioning, Disability and Health (WHO ICF) which recognises the biopsychosocial model as a model of disability (359). With chronic disease accounting for most of the morbidity, there is an urgent need for a biopsychosocial approach to be robustly integrated into healthcare management. The biopsychosocial approach was intended to extend and not replace the biomedical model (360). The concept of patient-centred care which underlies the biopsychosocial model (361) was shown to improve outcomes (362). Nevertheless, this model has not yet influenced those responsible for organisation of services and budgets (358). This concept continues to influence some areas of medical practice such as rehabilitation (363), chronic pain services (364) and mental health (365). Biopsychosocial rehabilitation of chronic low back pain was found to have positive effects on pain, disability and work status compared to physical treatment alone, as shown by a systematic review of 41 randomized controlled studies conducted by Kamper et al. (364). There is support for the utility of the biopsychosocial model in headache although it is scarcely used (366-368).

Studies suggest the clinical usefulness of viewing headache from a biopsychosocial rather than a narrow biomedical perspective (369-372). The current management approach in CH consists in managing the acute attacks and offering preventative medication when appropriate (373). Apart from the severe pain, CH attacks carry a high suicidality compared to the interictal state (374). Due to intense pain and often unpredictable nature of attacks, patients frequently experienced difficulties at work and required sick leave (225). Although the comorbid psychopathology (374) and impact on social life among patients with CH are well documented (225), the biopsychosocial model is not implemented in CH.

5.4 CHIPS study

The CHIPS (Cluster Headache: Impact and Perception Study) used a qualitative approach to explore the perceptions, experiences and understandings of CH among participants with CH, GPs and neurologists. This semi-structured interview study was undertaken by an interdisciplinary research team comprised of a medical sociologist (LD) and neurologists working in different medical settings (AB, FA, KP, PJG). The interviews were conducted by a medical sociologist (LD) using an interview topic guide. I was involved in the CHIPS team from its inception and my role was to facilitate recruitment, working closely with the other members of the team. I worked closely together with LD on the iterative analysis that took place during the data analysis and I led the analysis on the challenges with the diagnosis of CH.

5.5 Methods

This section outlines the CHIPS study design, a semi-structured interview study with participants with CH, GPs and neurologists. The study setting, data collection and data analysis are presented further.

5.5.1 Study design

The study design consists in a qualitative research approach using semi-structured interviews to explore the experiences with CH among participants with CH, GPs and neurologists (375). The study was conducted and reported in accordance with the consolidated criteria for reporting qualitative research (COREQ) (376).

5.5.2 Setting and data collection

Patients with CH according to the ICHD-3b (272) were recruited from a tertiary centre in the north of England. GPs and neurologists were recruited from several primary and secondary care trusts in the North of England. GPs and neurologists received a personalised email with an invitation to participate in the interview. Face-to-face interviews were the preferred option, but telephone interviews were considered if the interviewees favoured this option (377). All interviews were conducted by a medical sociologist (LD). A topic guide was used, this was compiled on the themes identified through literature review and the clinical experience of the

research team. The interviews explored the following broad themes: experience/interest with CH, social and diagnostic history, relationship between primary and secondary care, delay in diagnosis, misdiagnosis and mismanagement, doctor-patient relationship (see Table 5.1 and Table 5.2)

Table 5.1. Extract from topic guide for participants with CH with illustrative questions

Social and diagnostic history
▪ How/when did they decide to go to see a healthcare professional (HCP)? ▪ What was the response of the HCP? ▪ Did worry play a part in recognition and response to symptoms?
Description of symptoms
▪ What is the nature of the pain and associated symptoms? ▪ How do they behave during an attack and deal with it? ▪ What triggers a CH attack, according to the patient?
Delays in diagnosis, misdiagnosis and mismanagement
▪ Thoughts on time to referral, investigations and diagnosis? ▪ Anything that HCP could have done differently? ▪ Was it first diagnosed as another disorder? ▪ What kind of treatment works?
Experience with CH
▪ Impact on life: at home; at work; social context ▪ Knowledge and understanding: Where does the patient get information from? How often are they looking for new information? ▪ Has the patient tried complimentary/alternative treatments?
Treatment in primary and secondary care
▪ Relationship with GP, how often does the patient visit, GP's knowledge on specific medication (oxygen, sumatriptan injections, verapamil) ▪ Relationship with the staff at the hospital: headache nurse, neurologist, etc. ▪ How often does the patient go to the hospital in relation to CH?
Raising awareness of CH
▪ What is the most effective way to raise awareness around CH? ▪ Does the patient feel there is enough information available (for employers, friends/family, etc.)?

Table 5.2. Extract from topic guide for GPs and neurologists with illustrative questions

General knowledge about CH
▪ Do you see patients with CH in your practice? ▪ What is the nature of their pain? How do they describe it? What symptoms? ▪ How does it impact on patients' lives?
Diagnosing CH
▪ Do you feel confident in making a CH diagnosis? ▪ What kind of questions do you use in taking a diagnostic history? ▪ Do you use the current (or are you aware of) ICHD-3 criteria for CH?
Relationship between primary and secondary care
▪ What types of patients are referred to secondary care? ▪ How is the communication between primary and secondary care? ▪ What are the challenges and opportunities in your view regarding the relationship between primary and secondary care?
Treatment of CH
▪ What are the medicines for the treatment of CH you are familiar with? ▪ Are you aware of the use of oxygen and sumatriptan injections in the treatment of CH? ▪ Are you confident in prescribing preventive medicine such as verapamil and lithium?
Raising awareness of CH
▪ How can we raise more awareness of CH in primary care? ▪ How can we acknowledge the impact of headache disorders, in particular CH?

The interviews were recorded with permission of the interviewees and fully transcribed. Data collection was discontinued when data saturation was reached, which meant that no new themes were identified (378, 379). Data saturation was reached after 42 interviews (26 interviews with CH participants; 16 interviews with healthcare professionals) and no further interviews were conducted.

5.5.3 Data analysis

The data analysis consisted of two main parts: (1) to summarise the interviews of the CH participants into 26 diagnostic journeys of up to 350 words; and (2) a thematic analysis based on the principles of grounded theory (380). The analysis was carried out using QSR NVivo 12, a software package to analyse qualitative data (381, 382). The analysis was focused on the diagnosis of CH with emphasis on the diagnostic journeys. The interview transcripts were first read in full by AB and LD to gain an overall perspective of the data. A preliminary coding

scheme was developed and the interview transcripts were then coded thematically line-by-line by AB and LD. Other members of the research team (FA and KP) read a number of interview transcripts each and discussed these in detail with AB and LD. In case of disagreement between the researchers, consensus was reached upon discussion with other members of the team. The detailed coding framework was refined in a next phase when the overarching themes were identified.

5.6 Results

Here, I present the results of the qualitative data analysis on participants with CH, GPs and neurologists. This section includes participants' profiles in the CHIPS study, followed by mapping out the 26 diagnostic journeys of the CH participants. This results section continues with presenting the four main themes around the diagnosis of CH.

5.6.1 Research participants' profile in the CHIPS study

Forty-two respondents were interviewed (26 participants with CH and 16 clinicians: eight GPs and eight neurologists). Their profile is presented in Table 5.3, Table 5.4 and Table 5.5. Sixteen participants with CH were males and 10 females. Mean age of CH participants was 42. Ten clinicians were males (three GPs and seven neurologists) and six were females (five GPs and one neurologist). Mean age of clinician respondents was 49 (GPs = 47, neurologists = 51). Six out of 16 clinicians had a special interest in headache. The mean length of the interviews was 42 minutes.

Table 5.3. Neurologists' profile in the CHIPS study

Participant no	Gender	Age	Special interest in headache
N1	Male	54	Yes
N2	Male	56	No
N3	Male	48	Yes
N4	Male	43	No
N7	Female	52	No
N6	Male	55	No
N7	Male	59	No
N8	Male	40	Yes

Table 5.4. GPs' profile in the CHIPS study

Participant no	Gender	Age	Special interest in headache
GP1	Male	55	Yes
GP2	Female	55	No
GP3	Male	57	No
GP4	Female	52	Yes
GP7	Female	39	Yes
GP6	Female	34	No
GP7	Male	45	No
GP8	Female	38	No

Table 5.5. CH participants' profile in the CHIPS study

Participant no	Gender	Age	Type of CH	Employed
P1	Male	37	CCH	No
P2	Male	34	ECH	Yes
P3	Male	40	ECH	Yes
P4	Male	52	CCH	Yes
P5	Male	50	CCH	Yes
P6	Male	65	CCH	Retired
P7	Male	52	ECH	Yes
P8	Female	46	ECH	Yes
P9	Female	34	CCH	Yes
P10	Male	37	CCH	Yes
P11	Female	40	ECH	Yes
P12	Male	54	CCH	No
P13	Female	49	ECH	Yes
P14	Male	47	CCH	No
P15	Female	32	CCH	Yes
P16	Male	43	CCH	No
P17	Male	49	CCH	Yes
P18	Male	49	CCH	Yes
P19	Male	49	CCH	Yes
P20	Female	30	CCH	No
P21	Male	37	CCH	Yes
P22	Female	62	CCH	Yes
P23	Female	54	CCH	Yes
P24	Female	87	CCH	Retired
P25	Male	25	ECH	Yes
P26	Female	40	ECH	Yes

Abbreviations: P: participant; ECH: episodic CH; CCH: chronic CH

5.6.2 Twenty-six diagnostic journeys of CH

I summarised the interview data of the CH participants into 26 diagnostic journeys in order to map out different experiences of the CH diagnosis. Several participants related the onset of the CH attacks to recent head, neck trauma or teeth extraction which was a contributing factor to delayed diagnosis, although minor compared to clinicians' factors. The time from disease onset to correct diagnosis varied from a few months up to 39 years, according to the qualitative data. GPs' level of awareness of CH correlates with the time to diagnosis. Most of the diagnostic journeys of CH are characterised by multiple visits to the GPs or consulting different GPs without reaching a diagnosis, *'I must have seen every GP at least two or three times'* (P4, male, 52), said one interviewee. Most of the participants were diagnosed as migraine and were treated with migraine specific medication which are ineffective for CH attacks. When the participants self-diagnosed through online diagnostic tools, some were referred to secondary care services and others were denied the access to correct management. Desperate to obtain pain relief, CH participants administered overdose of painkillers, tried illicit drugs or self-harmed, *'tried to knock myself unconscious'* (P1, male, 37), said one participant. Most participants feel that they were not listened and their complaints were not taken seriously, '*he* [GP] *was kind of treating me as I was wasting his time'* (P16, male, 43), mentioned one of the respondents. Convinced they were misdiagnosed and mismanaged, some CH participants persuaded their GPs to obtain a referral to the neurological services. Here is how a CH participant described the encounter with his GP:

> You will refer me to a neurologist and you'll do it urgent because I can see a mark in the box and it says routine I haven't slept for a month now. I can't work. (P10, male, 37)

Due to delayed diagnosis and ineffective management, CH attacks had a significant impact on social life in most participants, some were reluctant to socialise and others lost their jobs. *'I'm not in that job anymore, I actually lost it because of the cluster headaches, because doctors messed me around'* (P25, female, 25), said one of the participants. The diagnosis was established by a neurologist in most cases, which was delivered after a brief history taking, *'I went to see a specialist (...) and literally within two minutes he said you've got cluster headaches.'* (P5, male, 50), as one participant mentioned. On a few occasions, GPs suggested the diagnosis of CH which facilitated access to secondary care and appropriate management, '*actually he picked up on cluster headaches, he actually mentioned cluster'* (P17, male, 49),

said one participant. Other respondent was pleasantly surprised when the diagnosis was mentioned by the dentist, where she presented with teeth pain.

Below, I present examples of three distinct diagnostic journeys experienced by the CH participants: a 30-year old teaching assistant diagnosed by her dentist, a 54-year-old male who self-diagnosed and a 47-year-old male who waited almost 40 years for a correct diagnosis.

(1) The diagnostic journey of CH participant no 9

One 30-year-old participant (P9) who worked as a teaching assistant experienced toothache one summer holiday. She received treatment for an abscess and had one tooth pulled but that did not seem the be the cause of the pain. Her GP said first she had an ear infection, but then changed his mind and thought it was trigeminal neuralgia. Here is how she recalled her diagnostic journey:

> I was backwards and forwards to the doctor, to the dentist, just help me please because I've got constant pain and it gets worse at certain times and it was always around teatime. (P9, female, chronic CH, 34)

She mentioned pains in her eye, jaw, teeth and ears. The GP confirmed the diagnosis of trigeminal neuralgia. Because her toothache continued she went back to the dentist. It was another dentist who, after she listed her symptoms, diagnosed her with CH: *'My dentist knew. He was amazing and I went home and I read about it and, it fits so well.'* P9 explained that the dentist heard about CH, found it interesting and read up on it. She visited her GP who admitted not knowing about CH. The GP left the consultation room, printed information about CH and came back in the room: *'I'll never forget the look on her face when she just said "oh you poor thing"'*. The GP took her straight off the antiepileptic medication and prescribed verapamil and triptan nasal sprays and referred her to the local neurology department. She explained it as follows:

> There are three or four different doctors that I see at my practice and they have all been amazing, really amazing, they have looked into things, they have been led completely by the headache specialist nurse and the headache neurologist. (P9, female, chronic CH, 34)

(2) The diagnostic journey of CH participant no 12

One-54-year-old male (P12) was a long-term heavy drinker without a prior history of headaches. P12 described '*completely blinding headaches',* two months after he had two teeth removed. The headaches were triggered by alcohol, always the same amount, *'after drinking one and a half pints of beer'.* His GP did not recognize the symptoms, which '*should have been red flags to a bull'.* Here is how he described his headache attacks:

> You get to this point where it's almost philosophical. You know, you've had me, this is death (…) you've already admitted to yourself death is the best thing' (P12, male, chronic CH, 54)

P12 saw numerous GPs who prescribed multiple painkillers and was told not to drink alcohol. He thinks that the doctors should have been able to make a diagnosis, '*the doctor should know, how the hell do I know?'* He went to the dentist who could not recognize the condition. Then, P12 researched his symptoms on the internet, '*I went on a symptom checker on the internet and bingo, cluster headache'.* He went to the GP and told about this diagnosis and the GP prescribed painkillers, '*more painkillers, head painkillers'.* He asked the GP about being referred to a specialist. The GP then decided to initiate verapamil after researching the treatment on the internet, '*he's* [neurologist] *going to prescribe you Verapamil, so let's put you on Verapamil'.* He was also started on verapamil without a baseline ECG check. Although verapamil reduced the intensity of the attacks, he suffered side effects, '*turned me into a vegetable, completely lethargic, couldn't do a normal life, couldn't do anything'.* He was not offered sumatriptan or oxygen, he used Red Bull as abortive therapy for 18 months that ceased the attacks within one minute. At his request, he was given sumatriptan nasal spray. P12 was suicidal and ended up in hospital inebriated. He was referred to the Pain Clinic instead of the neurological services where he was asked about formally being diagnosed with CH, *'she asked me, have I been diagnosed? I still can't fucking say, yes'.* P12 attended a seminar on headaches and asked the GP to be referred to one of the headache specialists that was present there. He was eventually seen by the headache nurse who formally diagnosed him. (P12, male, chronic CH, 54)

(3) The diagnostic journey of CH participant no 14

One-47-year-old unemployed male (P14) experienced severe headaches after a road traffic accident at the age of seven, *'I start punching my head, smashing my head against a wall and biting myself, whatever it takes to draw the pain away'*. P14 was very restless during the attacks and often hit his head against the wall, '*she* [mother] *used to come up and patch my face so after I'd been banging my face on the wall'*. His GP prescribed paracetamol and codeine thinking the headaches were migraine. This is how P14 described his diagnostic journey:

> I've been told that all, all my life, basically all my life, they're migraine, they're migraines, they're just headaches, and they've just been giving me different tablets. (P14, male, chronic CH, 47).

P14 tried cannabis once and has no relief from the painkillers prescribed by his GP. Here is how P14 described the impact of his headaches on his family life and mental health:

> What upsets all my family the most is the self-harming and the depression (…) I've had no support, anything, all I've been told by the GP, oh it's a headache, there you go and that's it'. (P14, male, chronic CH, 47)

His mental health worsened after his mother passed away when he started abusing alcohol. After many years of suffering, P14 was referred to a neurologist with special interest in headache and diagnosed CH and started him on appropriate management. The diagnosis came almost 40 years after the first symptoms (P14, male, chronic CH, 47)

5.6.3 Four main themes on the diagnosis of CH

In this section, I present four main themes on the diagnosis of CH that emerged from the interview data: (1) lay diagnosis; (2) delays in diagnosis; (3) misdiagnosis and mismanagement, and (4) establishing the correct diagnosis. In Figure 5.1, I summarise the four main themes on the diagnosis of CH.

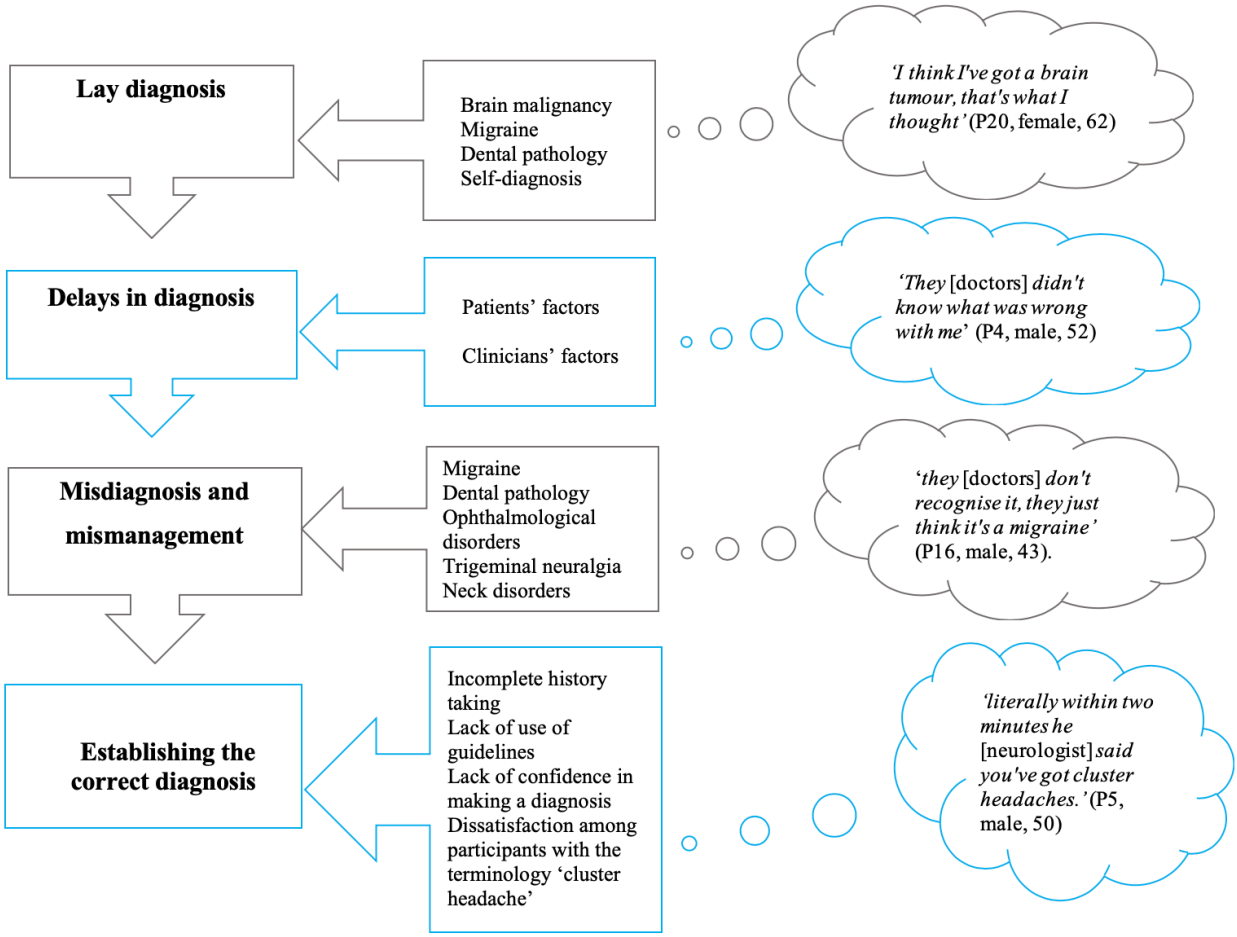


Figure 5.1. Summary of the four main themes on the diagnosis of CH

5.6.3.1 Lay diagnosis

Here, I outline four main results regarding the lay diagnosis including malignancy, migraine, dental pathology and self-diagnosis of CH.

Brain malignancy

Many participants with CH were concerned about having a life-threatening condition such as a brain tumour when they experienced the first CH attack, '*freaked me out a bit thinking oh it might be a tumour'* (P10, male, 37). The experience of severe pain determined one participant to make '*a new will'* (P22, female, 62), as she assumed she had a malignant condition.

> I went to bed one night, woke up about two or three o'clock in the morning, early hours of the morning, the most horrendous headache I've ever experienced in my life, thought I was having some sort of brain tumour. (P11, female, 40)

Migraine

Some interviewees confused the severity of the attacks with migraine-like symptoms, '*I just thought it was a bad migraine'* (P15, female, 32). Others recognised that the intense severity of the attacks is atypical for a regular headache or migraine and sought medical help in order to get diagnosed, '*it's not like a headache, it's nothing like a headache'* (P17, male, 49). One CH participant feared a brain infection due to the aggressive headache symptoms *'have I got meningitis? What going on?'* (P11, female, 40).

> This is not migraine, migraines don't last days and days on end, migraines do make you sick, yes (…) I mean even if I go in a dark room (…) I'm still fidgeting and can't keep still, all I want to do is just put my head against a wall. (P23, female, 54)

Dental pathology

The pain radiating to the mandibular area was regarded as a symptom of dental disorders by some interviewees. Due to the constant unremitting pain, a suspicion of a tooth or ear infection determined some CH participants to seek medical advice from ENT specialists or dentists. '*I just thought it was a really bad ear infection or a tooth infection',* mentioned one of the participants (P9, female, 34).

Self-diagnosis

The access to digital information facilitated some interviewees to self-diagnose. This was a result of multiple visits, distrust in the health professionals and the lack of effective treatment, according to some participants.

> GPs, they're too busy. They don't want to actually help you, if they don't know what it is, fair enough, they'll try and give you some painkillers, which aren't going to do anything. I researched all the symptoms and to be honest with you one of the first things that came up was cluster headaches. (P25, male, 25)

5.6.3.2 Delays in diagnosis

This section presents the delay in diagnosis and factors involved in delays, including both clinicians' and patients' factors.

Clinicians' factors

Most respondents suffered for many years before the diagnosis was made, '*It was years, probably about ten years before the doctors did anything'* (P6, male, 65). One CH participant was suspected of exaggerating the severity of the headache, '*you're being dramatic, you know, it's a headache, people get headaches, you take some Paracetamol, you get on with it'* (P20, female, 30), one patient said about the GPs' reaction. Other GP wrongly considered that the CH participants is looking for a claim, *'he* [GP] *assumed that I was out for a claim'* (P1, male, 37), mentioned the respondent. Other interviewee explained that she visited seven different clinicians without obtaining a diagnosis: *'They couldn't come up with anything'* (P25, female, 25).

According to most study participants, GPs prescribed multiple painkillers as a way of dealing with the consultation, *'they give me more headache tablets and migraine tablets'* (P2, male, 34). Multiple respondents were prescribed painkillers repeatedly despite the lack of response, '*here's a painkiller and I was doing that for years'* (P16, male, 43). One CH sufferer complained of the poor history taking and superficial medical approach when managing his headache condition, '*they don't really ask questions*', said this participant about the GPs he consulted (P16, male, 43).

> They [GPs] don't really ask questions, you go in, you tell them that you've got pain in your head, coming from like your temples and they just say oh here's a migraine tablet, here's an Anadin, and aspirin (…) I went through every painkiller on the market before he actually sent me to hospital. (P16, male, 43)

According to the interviewees, many clinicians are consulted before the correct diagnosed is established. It is usually their GP that is visited multiple times, '*kept going backwards and forwards to my GP*' (P4, male, 52). Some CH participants reported asking for a second opinion or changing the GP practice '*I* [patient] *changed doctor surgeries and I went to the new one'* (P20, female, 20). Many CH participants mentioned visiting the A&E departments during the CH attacks. In most cases, CH was not recognised by the A&E doctors and it was poorly managed. One respondent was told '*why don't you just take Paracetamol, it's only a headache'* (P4, male, 52). Some clinician-participants acknowledged that the referrals to other specialities such as ENT and having invasive procedures delayed the diagnosis. Delays in diagnosis as long as fifteen years have been mentioned by the clinicians. One neurologist acknowledged that the short consultation time prevent GPs to take robust history which contributed to missed and delayed diagnosis.

> I take the history, they have cluster headache and then I find out that they have had these headaches for fifteen odd years, one because they go away after a few weeks so therefore they are episodic, that's why I think they would have seen many different GPs. (N1, male, 54)

Delays in diagnosis and misdiagnosis also occur due to inappropriately short consultations in both primary and secondary care. One GP interviewee felt that primary headaches are not prioritised once secondary headaches are ruled out. Same GP mentioned that other GP colleagues '*wouldn't be very happy about dealing with it, that's the, sort of the culture'* (GP1, male, 55). One neurologist explained the same about some of his neurology peers who do not regard primary headaches as a serious illness. Headache consultations are seen as '*time savers',* as he puts it (N1, male, 54). This neurologist thinks that other neurological conditions such as multiple sclerosis, Parkinson's disease or motor neurone disease are offered more time during consultations in the detriment of patients with headaches. Furthermore, one neurologist feels that the headache medicine is neglected by both clinicians and researchers. According to him,

few clinicians have an interest in headache and a small number of neurology trainees pursue headache research.

> If you've got eight patients in the clinic, the neurologists tend to get the headache patient out within five minutes, just quickly asking them two or three questions, giving them a prescription or whatever and save that time for people who have multiple sclerosis, Parkinson's, motor neurone disease, stroke and other things. (N1, male, 54)

Patients' factors

In some cases, obtaining a correct diagnosis was delayed because sufferers feared of being stigmatised, as they were *'embarrassed to tell anybody'* (P1, male, 37). Lack of awareness or uncertainty about the meaning of symptoms were other factors that contributed to delayed diagnosis as CH participants '*ignored it'* (P17, male, 49). These were mostly participants with episodic CH with long periods of remission that did not consult the medical services. Other CH respondents had the tendency to normalise their symptoms: '*I just thought it's a headache'* (P10, male, 47). Many CH participants delayed seeking medical help as they thought were suffering from migraine, or had a relative who had migraine and suggested this diagnosis to them.

5.6.3.3 Misdiagnosis and mismanagement

This section presents the misdiagnosis and mismanagement of CH participants on their journey to correct diagnosis.

Misdiagnosis

According to data analysis, most CH participants in this study were misdiagnosed as migraine. Furthermore, both GPs and neurologists mentioned migraine as the most common misdiagnosis of CH. Clinicians felt that '*people tend to label every headache as a migraine'* (N1, male, 54) as it is one of the most common headache disorders. Most CH participants claimed that the GPs did not recognise the typical symptoms of CH, '*they don't recognise it, they just think it's a migraine'* (P16, male, 43). Some CH interviewees questioned the GPs' diagnosis, *'this is not a migraine, this is definitely not a migraine'* (P23, female, 54). According to many CH participants, GPs persevere in making the same diagnostic error for many years.

> My mum phoned the doctor, he came out, he said she's got a migraine, put a towel over her head, give her some Paracetamol, let her sleep and she'll be fine. (P20, female, 30)

According to the interviewees, CH is also misdiagnosed as sinusitis, dental disorders, TTH, ophthalmological disorders, trigeminal neuralgia, medication overuse and neck disorders. Some CH participants believed that their attacks might be secondary to dental disorders and considered appropriate to seek medical help from dentists. They mentioned pain radiating to the maxillary or mandibular area. Others had their teeth removed despite no obvious dental pathology. According to CH participants, multiple diagnoses were received before CH was recognised, '*they thought it was ingrown eyelash'* (P24, female, 87). Other respondents were diagnosed as trigeminal neuralgia, '*GP diagnosed it as neuralgia'* (P7, male, 52). Anxiety, sinusitis and ear infection are other misdiagnosis mentioned by the CH participants, *'I had everything suggested to me*' (P2, male, 34).

> The [doctors] were saying it was either sinusitis or a migraine or I was getting both at the same time. (P6, male, 65)

Some neurologists considered that the lack of awareness of mixed syndromes (e.g. CH and migraine) contributes to misdiagnosis as patients do not present '*as the textbooks'* (N8, male, 40). Most neurologists identified that the presence of background pain outside the CH attacks leads to misdiagnosis. Analysis showed that unilateral headaches are often perceived as migraine, '*unilateral headaches are migraine until proven otherwise'* (N4, male, 43). Clinicians commented on the unnecessary procedures undertaken by patients with CH such as teeth extraction or sinus washout before the correct diagnosis was received.

> I was embarrassed by one woman who is a neighbour who, we were constantly saying she had sinus infection and one of our locums sort of pointed out this is a cluster headache and he's absolutely right. (GP3, male, 57)

According to some research participants, they did not feel understood by the GPs, '*I didn't feel as though I was taken seriously'* (P25, female, 25) or they are considered to be '*dramatizing things'* (P20, female, 30). Some patients mentioned that GPs '*don't really ask questions'* (R16, male, 43) and are preoccupied to save time in clinic,'*if they can get you out before the ten, fifteen minute slot'* (P19, male, 49). Some research participants felt that CH is perceived as

'*several attacks of headache close together'* (GP1, male, 55). A confusion between the terms 'cluster headache' and 'cluster migraine' was believed to contribute to misdiagnosis, according to some clinicians.

> The commonest people I get referred from GP about cluster headache is people who've had three migraines in a week…Well some use the word cluster migraine. (N2, male, 56)

Mismanagement

According to data analysis, patients with CH often had unnecessary procedures performed such as teeth extraction or sinus washout. Clinicians mentioned patients misdiagnosed as trigeminal neuralgia that had microvascular decompression when in fact they had CH that responds to non-invasive treatment.

> They [patients] have had their head open and do microvascular decompression surgery and then they didn't get better and then they came to my headache clinic and I said well he didn't have trigeminal neuralgia, he had cluster headache. (N1, male, 54)

5.6.3.4 Establishing the diagnosis of CH

Here, I present the fourth theme, establishing the diagnosis of CH. Five main sub-themes emerged from analysing this theme: (1) history taking; (2) the use of guidelines in making a diagnosis; (3) confidence in making the diagnosis; (4) clinicians that established the diagnosis, and (5) challenges with the terminology 'cluster headache'.

History taking

According to most GPs, the history taking was concentrated on excluding secondary headaches by ruling out '*all the red flags'* (GP4, female, 52). Inquiries about previous head injury, the presence of visual deterioration, fever, rash are part of the history taking in primary care, as mentioned by some GPs. Some interviewees felt that some headache features are not *'necessarily volunteered*' (GP1, male, 55) during the history taking such as the presence of cranial autonomic symptoms and the behaviour during attacks. One study participant mentioned that once a secondary headache was ruled out, '*people prioritise it less'* (GP1, male, 55). CH was perceived as uncommon by many participants, in particular GPs, were not aware of the associated clinical symptoms. GPs were not confident in diagnosing CH. Neurologists

pointed at the lack of robust history taking when patients presented with headache symptoms in primary care:

> I am very much interested to know, why does it take too much time to make a diagnosis of cluster headache? And it is such a painful condition and I want to know is it something that the patient doesn't describe? Is it something that the GPs don't listen? Is it something that the GPs don't ask? (N1, male, 54)

The use of guidelines in making the diagnosis

Some GPs were not familiar with the ICHD-3 criteria for CH diagnosis and others have '*not really had any idea of where to look for things'* (GP1, male, 55). Some research participants mentioned the necessity of information that is '*readily accessible*' (GP1, male, 55). NICE guidelines were considered by one of the participants as being '*quite lengthy'* (GP3, male, 57) and '*hard to navigate it in a busy clinic'* (N7, male, 59).

Confidence in making a diagnosis

Some GPs felt lack of confidence in making a CH diagnosis. They occasionally recommended brain scans not to miss '*anything intracranially'* (GP4, female, 52*)*. Others mentioned being more confident in making a diagnosis when the clinical picture '*it's absolutely classical'* (GP3, male, 57)

> I may feel that I'm eighty percent confident (…) unlike with migraine, I always get a bit twitchy just because of the severity of the pain. (GP4, female, 52)

Clinicians who established the diagnosis

Most CH participants were diagnosed by a neurologist. They felt that the neurologists made a rapid diagnosis with no difficulties in recognising the condition, '*he diagnosed me within ten minutes'* (P26, female, 40). According to CH respondents, neurologists required a brief history before establishing the correct diagnosis, *'she diagnosed me straightaway'* (P16, male, 43).

> It was about a minute. He [neurologist] said, just talk to me, I started talking to him like, he went, cluster headaches. (P19, male, 49)

Challenges with the terminology 'cluster headache'

Some participants with CH felt that the condition is not taken seriously because the terminology contains the word '*headache*'. One participant thinks that CH should be named '*cluster agonies'* (P6, male, 65). Other interviewees with CH refer to their attacks as '*killer headaches'* (P6, male, 65) or '*completely blinding headaches'* respectively (P12, male, 54).

> I think cluster headaches is a ridiculous name for this condition, absolutely ridiculous, it is nothing at all like a headache, this pain is more like having your legs amputated without any anaesthetic. (P13, female, 49)

One participant suggested that the previous terminology, Horton's neuralgia is more appropriate than 'cluster headache' as it does not contain the word 'headache'. He considered that a different terminology could change peoples' perceptions and possibly eliminate the stigma attached to it. Employers have difficulties understanding the severity of the condition because of how it is named, as mentioned by one participant.

> I mentioned it to my new boss, when I said cluster headaches he thought 'oh headaches,' that was his exact response. I was like no, it's worse than migraines, he was like okay. He literally rolled his eyes. (P25, male, 25)

5.7 Discussion

In this section, I will interpret the results presented above by discussing and contextualising my findings in the sociological literature. I first discuss the perceptions of CH diagnosis among clinicians and further address the factors involved in the diagnostic delay. I conclude with a section on the strengths and limitations of this study.

5.7.1 Perceptions of CH diagnosis among clinicians

Despite headache being the most common cause of neurological referrals (383), diagnosing primary headache remains challenging for GPs (384). Good knowledge of primary headaches among GPs is paramount as the majority of headache presentations are managed in primary care and only 2-3% are referred to specialist services in neurology (385). The diagnostic journey of CH begins with the patients' first symptoms and ends when a correct diagnosis is

established. While this happens for common ailments, less common often have neither a smooth nor a short diagnostic journey (386).

According to our qualitative data, CH is perceived as a rare disease although its prevalence (1/1000) (5) is similar to that of other neurological conditions such as multiple sclerosis (0.9/1000) (387) and Parkinson's disease (1-3/1000) (388). The strategy of therapeutic trial or 'watch and wait' applied usually in primary practice could be detrimental to less common conditions such as CH (389). According to the existing literature, GPs considered it less relevant to make a specific diagnosis and used the course of time as main diagnostic tool (390). This strategy could be harmful for patients with CH as referrals to neurological services were significantly delayed in the current study and obtaining a diagnosis took as long as 39 years. Despite lack of response to treatment, frequent medical visits and challenged diagnosis, GPs in our study have not reconsidered their initial diagnosis of migraine. This suggests poor awareness of uncommon, although not rare headache syndromes, such as CH.

Current measures of quality of care in primary care are not focused on diagnostic delays and errors (391). As a consequence, significant diagnostic delays of CH and consulting multiple health professionals causes a substantial and avoidable burden on the health system (64). Misdiagnosis can be prevented by access to GPs with special interest which decreases the waiting time, referrals and cost (392). It is important that GPs are aware of this condition and it is not seen as a Cinderella disease (40).

In the next section, I describe the social impact of CH in the context of prolonged diagnostic journey, drawing from the medical sociological concepts presented in section 5.3.

5.7.2 The impact of CH

Primary headaches have been scarcely represented in the social scientific literature despite their high prevalence and major cause of disability (337). Sociologist Kempner, who focused her work on the gender dimensions of migraine (294, 332) and CH (293), examined migraine-associated stigma which acts as a barrier to seek healthcare (294). On the one hand, our findings show that some patients avoided to seek medical advice due to the risk of being discredited. Many patients felt that their physical complaints were not given the necessary attention by the medical professionals they consulted. Some patients challenged the diagnosis received and treatment recommended. Many CH sufferers brought a lay diagnosis to the consultation as they had 'googled' their symptoms prior to seeking medical advice. This is consistent with Jutel's

work on self-diagnosis using medical information available digitally, where she described reconfiguring of doctor-patient relationship due to wide access to medical information (338). The availability of medical knowledge reduces the autonomy of the medical professional and reshapes the doctor-patient interaction (338). Our findings indeed confirm that frequent encounters between CH sufferers and GPs, a lack of diagnosis and, as a consequence, lack of effective treatment pathways negatively affect the doctor-patient relationship. As shown by the sociological literature and confirmed by the findings in this study, lay people are ready to challenge their doctor and seek advice outside the doctor-patient relationship (347). Participants with CH in the current study were ready to contest the diagnosis of migraine and many self-diagnosed using online information. Clinicians should embrace the internet usage, offering patients more autonomy and agency (349). Therefore, adopting a model of mutuality rather than a paternalist approach of medical practice could be beneficial for the doctor-patient relationship during headache consultations (342). A patient-centred approach has a positive influence on the doctor-patient relationship, improves health care outcomes and the use of health resources (393). Patients' outcome could be improved by designing an individualised management plan for CH including timely referral to specialised centres for confirmation of diagnosis and inquiries into the impact on mental health and social life.

Our findings clearly show that patients with CH are in 'diagnostic limbo' for a long time (338, 340). This period where patients live without a clear diagnosis often has significant implications for mental health (394), social and work roles (330). Psychiatric comorbidities such as suicidal ideation, depression, anxiety and panic attacks are indeed prevalent among patients with CH (395). Patients with CH have difficulties at work, require frequent sick leave and have low engagement in social activities (225). The lack of a correct diagnosis denies patients access to appropriate treatment, support groups and, if applicable, disability payments and sick leave (42). Our data highlight that CH sufferers, during their diagnostic journey, make frequent visits to hospital, try numerous inappropriate treatments and consult multiple clinical specialists. This often leads to distrust in the medical profession and seeking alternative therapies (331). Although the management is unique among primary headaches, CH can be successfully treated with symptomatic therapies. The acute treatment with high flow oxygen or sumatriptan subcutaneous injections/nasal spray or preventative therapies (e.g. verapamil, lithium, melatonin) are widely accessible (373). Migraine, the most common misdiagnosis of CH according to our qualitative data, denies patients access to correct management of a treatable condition. Patients with CH often experience difficulties of living with uncertainty and dealing with legitimacy, which is a consequence of medically unexplained or undiagnosed

symptoms (338, 341). The diagnosis is a label that legitimises the illness, as Jutel clearly concludes in her book (338). Patients with CH experience prolonged diagnostic odysseys in search for a diagnostic label that confers legitimacy and enables access to privileges such as medication or sick leave (338). Some CH participants in our study felt *'awarded'* when a correct diagnosis was established as it enabled access to appropriate management (338). Due to how the condition is named, other participants felt '*branded*' and stigmatised as they were not understood by their family members or employers (338).

In view of the unpredictable pattern of CH and early age of onset (mean age 30.2 ± 13.8 years) (396), one can envisage CH as a highly disruptive illness especially in young individuals. Furthermore, due to the nature of the disease with frequent disabling attacks, patients with CH are unable to sustain their daily activities and to remain in employment (225). The data analysis demonstrates profound biographical disruption in the study participants, especially those with multiple untreated daily attacks. The data show that this often leads to deep emotional distress and need for urgent medical attention (395). Such biographical disruption in CH can explain the prevalence of suicidal ideation and suicide attempt in CH sufferers, which has been reported in the clinical literature (374, 394, 395). In the context of chronic illness, people face narrative reconstruction, which represents a 'story' of their illness that enables them to make sense of their life (397). Similarly, one participant in the CHIPS study, made a new will due to experiencing severe headaches as she thought of having a brain malignancy. Biographical disruption and narrative reconstruction could be powerful tools to understand the psychological and social context of CH which can have implications for management.

Primary headaches are currently managed with symptomatic treatment (240). Due to psychological factors triggering primary headaches and associated psychiatric comorbidities, biopsychosocial approach was experimented with success in children with chronic daily headache and migraine patients (369-372). The current management of CH consists of symptomatic treatment with high flow oxygen and sumatriptan subcutaneous injection/nasal spray as abortive therapy and preventative treatment (e.g verapamil, lithium, melatonin) if indicated (373). Due to severe headache attacks, increased ictal suicidality including passive and active suicidal ideation, suicidal planning and attempt was found in patients with CH compared to interictal periods (374). Furthermore, patients with CH have difficulties at work and often are unable to remain in employment (225). Therefore, I suggest a biopsychosocial approach as opposed to the biomedical model currently implemented in CH given their significant psychiatric comorbidities (395) and important impact on social and work life (225). Setting up a multidisciplinary team with specialists in headache, neuropsychologists,

occupational therapists with the goal of addressing the physical, environmental and psychological factors may improve the management of CH sufferers.

5.7.3 Factors contributing to delayed diagnosis of CH

Multiple factors involved in the prolonged diagnostic journey of CH emerged from the qualitative data. A summary of these factors is presented in Figure 5.2. Although the diagnosis of CH in this study was delayed as some patients did not seek timely medical help, clinicians had a greater impact on the delays in diagnosis, which is consistent with previous studies (14, 41). According to the qualitative data, patients first present to their GP surgeries or emergency departments. Even though GP gatekeeping acts as a filter that should reduce unnecessary procedures and adverse events (226), patients with CH are underserved by the medical system, facing long delays in diagnosis, unnecessary referrals and avoidable procedures (398). Other conditions such as cancer face delays in the diagnosis (399, 400) as a limitation of the gatekeeping system when uncommon conditions present with common symptoms (228). There are conflicting views of the importance of the exact diagnosis in primary care in patients with headache (390) as many patients have a self-limiting headache of benign origin (389). Within NHS, the primary point of contact are GPs who select patients that need specialised care from those who are managed in primary care (227). As a consequence, patients that are not recognised in primary care do not have access to specialised treatment in a headache centre.

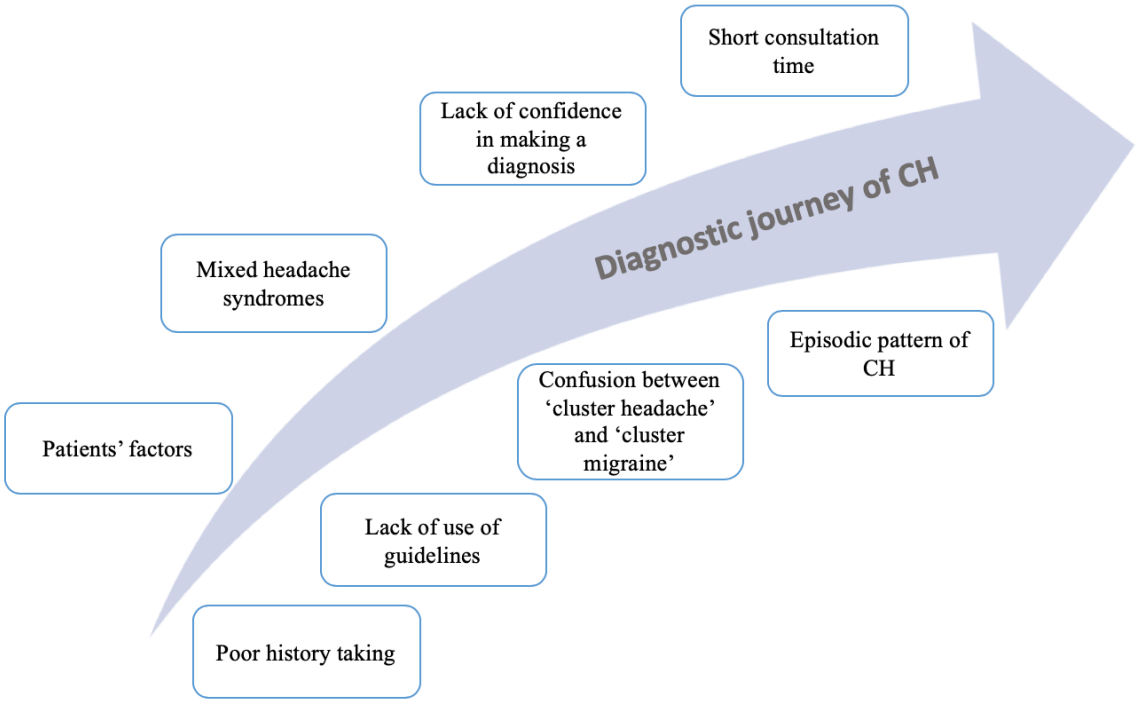


Figure 5.2. Factors involved in the prolonged diagnostic journey of CH

The current literature reports migraine as one of the most common misdiagnoses (14, 15, 51, 59), shown by the qualitative data too. GPs and neurologists think that CH is frequently misdiagnosed as migraine, a widely recognised primary headache among the general public and health professionals. Furthermore, some patients themselves thought they might have migraines. CH and migraine share common features (303) which was shown to play a role in misdiagnosis (59). Other misdiagnosis previously described include trigeminal neuralgia (14, 15, 41, 51), TTH (14, 16, 41, 59), dental pathology (14, 15, 41, 51, 54), ENT (14, 16, 51, 57) and ophthalmic disease (14, 51). Misdiagnosis extend to other more common primary headaches such as migraine, frequently misdiagnosed as sinusitis (401). This suggests that a low prevalence is not solely involved in the misdiagnosis of primary headaches. Disclosure by patients of their ideas, concerns and expectations about diagnosis or treatment was associated with less medication prescribing in primary care (402). However, GPs initial diagnosis of migraine was not reconsidered when this was challenged by the CH participants.

The short consultation time and poor history taken by GPs mentioned by some CH participants could have contributed to delayed diagnosis and misdiagnosis of CH. This interview study showed that characterising a primary headache is less of a priority in primary

care once a secondary headache was ruled out. It was previously shown that under time pressure, GPs asked less questions concerning presenting symptoms, than the ones indicated by the guidelines, conducted a less-thorough clinical examination, while they gave less advice on lifestyle (403). According to our data, the presence of mixed syndromes (e.g. CH and migraine, CH and TTH), confusion between the terminology CH and cluster migraine, the presence of an episodic pattern, represent factors that could have contributed to missed and delayed diagnosis. This is similar to previous studies that reported the presence of episodic CH and interical headache as a contributor to delayed diagnosis of CH (54).

Some GPs felt lack of confidence in diagnosing CH, as shown by the qualitative data. This is in keeping with other studies that found that GPs lacked confidence in diagnosing other conditions such as dementia (404) or managing obesity (405). Our study showed little usage of NICE guidelines in the clinical practice due to their length and complexity. NICE guidance has limited impact on GP prescribing such as prescribing antivirals (406) or chemoprevention for breast cancer (407). Some study participants expressed a need for easily accessible guidelines which is consistent with other studies (408). Reports showed that GPs were more likely to use guidelines where evidence was applicable to primary care, and less likely if the evidence base came from a secondary care populations (408).

Diagnostic journeys of CH finalised with consulting neurologists who made the correct diagnosis in most cases. Some participants with CH were unsatisfied with the disease terminology 'cluster headache' that, in their opinion, does not capture accurately their experience of intense pain and agony. Some CH participants felt that the disease name does not legitimise this serious medical condition. 'Cluster headache' is the current accepted terminology according to ICHD-3 criteria (1). For many years, CH was known under multiple different names including periodic migrainous neuralgia of Wilfred Harris, erythroprosopalgia of Bing, ciliary neuralgia, Horton's headache, eritromeralgia of the head, histaminic cephalalgia, Sluder's syndrome, hemicrania angioparalyticia, petrosal neuralgia, sphenopalatine neuralgia, vidian neuralgia or Sluder's neuralgia (409). The condition was previously thought to be a variant of migraine (410). With the significant progress on understanding primary headaches' pathophysiology including functional imaging research (37), the opinion has shifted from regarding CH as a migraine variant. I support patients' views whereby the disease terminology should accurately reflect their pain experience, in order to feel understood and accepted by society.

5.7.4 Strengths and limitations

This is the first qualitative study on CH which includes a robust sample of CH participants, GPs and neurologists. The diversity of research participants aimed to capture the range of views on the understandings and experiences of CH diagnosis from both sides of the care. This is the first study of its kind to explore both CH participants' and clinicians' (GPs and neurologists) perceptions with regards to CH diagnosis. The interdisciplinary research team, led by an experienced medical sociologist (LD), comprised of a number of experienced headache specialists (KP, PJG, FA).

A limitation, characteristic for all qualitative studies, was that clinicians were informed in advance that they were taking part in a study on CH. It might be the case that they looked up some information about CH prior to the interview. Although this was not reflected in our findings as many clinicians were upfront and honest about their knowledge around CH. This study has not captured whether patients with a dual diagnosis of migraine and CH experienced longer delays in diagnosis. This research recognises the gender imbalance of the neurologist participants (seven males and one female) although this does reflect the reality of the gender gap in neurology (411). Although the gender dimensions among patients with CH is an important topic previously studied in the sociological literature, this was not among the aims of this study (294).

Below, I conclude this chapter with key findings of this interview study and main learning points relevant for the diagnosis of CH.

5.8 Conclusions

This chapter presents the methods of the CHIPS study, a qualitative semi-structured interview with participants with CH, GPs and neurologists. The analysis is focused on the diagnostic journey of CH from the perspective of three stakeholders: CH participants, GPs and neurologists. Drawing from medical sociological concepts, I theorise the social impact of CH including stigma, dealing with uncertainly, influence on self-perception and legitimacy of illness, biographical disruption, narrative reconstruction and doctor-patient tensions. Due to significant psychiatric comorbidity and social impact I suggest the biopsychosocial model as an alternative to the biomedical model in the management of CH. The diagnostic journey of CH participants included numerous GP visits, consultation of ENT specialists, dentists or

ophthalmologists. Multiple factors were involved in the prolonged diagnostic journey including patients' and clinicians' factors.

Chapter 6. General discussion and conclusions

6.1 Introduction

In this dissertation I examined the challenges around diagnosing CH in a timely way. CH is a severe primary headache, often missed and mismanaged. There is an urgent need for more timely diagnoses of CH and to ensure that patients with CH receive prompt and appropriate management, due to the high disease severity and disability. My doctoral project explored the diagnosis of CH using a multi-methodological approach, including both qualitative and quantitative research. The study consists of four main parts:

(1) a systematic literature review on the delays in diagnosis and misdiagnosis of CH;
(2) a literature review on the pathophysiology of CH;
(3) a prospective observational study whereby a screening tool for CH was developed and assessed;
(4) semi-structured interview study on the perceptions and understandings of CH diagnosis from three stakeholder groups: participants with CH, GPs and neurologists;

In this final chapter, I bring together my doctoral study's main findings. I first present an integrated overview of my findings. This is followed by a section where I outline implications for clinical practice and continue with both the strengths and limitations of my doctoral research. I conclude with a personal reflection and a section on future work.

6.2 Integration of findings

In this overview I draw together the findings of each arm of my doctoral research. Here, I present three main themes found among several chapters:

(1) Point of seeking healthcare
(2) Delays in diagnosis and factors involved in delays
(3) Obtaining correct diagnosis

The main themes and which chapter informed these themes are presented in Table 6.1.

Table 6.1. Integration of findings: common themes among several chapters

Theme and chapter	Point of seeking healthcare	Delays in diagnosis and factors involved in delays	Obtaining correct diagnosis
Systematic literature review (SLR)	Patients with CH in this SLR consulted multiple clinicians including GPs, ENT specialists, ophthalmologists, dentists, pain specialists and also A&E doctors, psychiatrists, and neurosurgeons (see Table 6.2). The first point of seeking healthcare was not captured in the studies included in this SLR.	The mean time to correct diagnosis varied from 2.6 to 9 years (42, 53). The mean number of diagnosis received per patient was 2.2 (41) and in other study was 3.9 (56). Two studies included in the SLR showed reduction in delays of CH diagnosis over time (42, 51). There are contradictory results on the influence of gender on delays (16, 42, 51). Both clinicians' and patients' factors are involved in delays (see Table 6.4).	Multiple specialists and many misdiagnoses were received before obtaining correct diagnosis (see Table 6.3 for types of misdiagnoses received). Patients consulted between 2-5 clinicians before the correct diagnosis was made (14, 15, 41, 51). Self-diagnosis was reported in several studies in the SLR (14, 41, 42). Neurologists established the diagnosis in most cases (14) but in other cases they missed it (51).
Literature review on the pathophysiology of CH	This chapter did not inform on the theme 'Point of seeking healthcare'.	The lack of biological markers in the diagnostic process probably contributes to delays.	This review showed that there are currently no specific biological markers that could be used in the clinical practice to aid the diagnosis of CH. Biological markers such us CGRP, VIP,PACAP-38 are increased in CH, but not specific for CH (121, 139, 140, 157, 165).

			Neuroimaging studies showed findings specific for CH but they are not available in the current clinical practice.
Quantitative study	This chapter did not inform on the theme 'Point of seeking healthcare'.	This chapter did not inform on the theme 'Delays in diagnosis and factors involved in delays'.	This study developed and tested a novel 12-item screening tool that could aid the diagnosis of CH (sensitivity 86.4% and specificity 92%).
Qualitative study	The first point of seeking healthcare for most patients with CH was primary care where they consulted their GPs. Some patients with pain radiating to their teeth visited dentists and others went to the A&E department. One patient was referred to the ophthalmology department. The diagnostic journey in this study included multiple visits to GPs, occasional dental procedures or visits to A&E departments. The diagnostic journey finalised with seeing neurologists in the public or private sector, who made the correct diagnosis.	Patients waited between 6 weeks and 39 years to obtain a correct diagnosis. Clinicians' factors are involved in diagnostic delays. Patients' factors were also present but have less impact on delays (see Table 6.4). Drawing from the sociological concepts, I theorised the impact of undiagnosed CH including impact on self-perception and identity, how others view the sufferer, legitimacy of illness, biographical disruption and biographical fracture. The challenges with diagnosis negatively influence the doctor-patient relationship. I put forward the biopsychosocial model of illness as opposed to the dominant medical model.	Neurologists made the diagnosis in most cases. In one case a neurologist missed the diagnosis. In a few cases, the diagnosis was suggested by GPs, A&E doctors and in one case, a dentist. Self-diagnosis with subsequent specialist confirmation was also present.

6.2.1 Point of seeking healthcare

According to both the systematic literature review and interview study in this doctoral project, patients with CH consulted different medical specialities before the correct diagnosis. Table 6.2 presents the points of seeking healthcare in the systematic literature review and qualitative data. The first point of seeking healthcare for most patients with CH is primary care, according to the interviewees in the qualitative study. Furthermore, patients with CH consulted their GP several times or different GPs from the same primary practice before receiving a correct diagnosis. Despite headache being the most common cause of neurological referrals (383), diagnosing primary headache remains challenging for GPs (384). There are conflicting views of the importance of the exact diagnosis in patients with headache (390) as many patients have a self-limiting headache of benign origin (389). GPs occasionally apply the strategy of therapeutic trial or 'watch and wait' which can be harmful to less common conditions such as CH (389). When consulted by patients with headaches, GPs considered it less relevant to make a specific diagnosis and used the course of time as main diagnostic tool (390).

Seeking healthcare behaviour is a result of gender, cultural, social, economic, organisational and geographic determinants (412). The qualitative data gives insight into patients' factors that influenced the first point of seeking healthcare. Lay diagnosis of migraine, dental disease or head trauma-related pain determined which doctors were first consulted. Patients with onset of symptoms after teeth extraction or those who had pain radiating to their teeth first consulted their dentist. According to the CH participants in the interview study, one dentist suggested CH as diagnosis and others performed invasive procedures in the absence of objective dental disease. In order to avoid diagnostic delays and unnecessary procedures, dentists should be aware of dental presentations of CH (413) and onset of CH following dental treatment (414). Clinicians who did not recognise CH occasionally referred patients to inappropriate specialties, further delaying the diagnosis. This was experienced by one interviewee who was referred to ophthalmology after attending the A&E department. CH can be successfully treated in the A&E departments with high flow oxygen and injectable triptans, if recognised (415). Around one third of the interviewees developed CH after head trauma or teeth extraction. Post-traumatic CH or onset of CH after head injury is a recognised clinical entity, often under-recognised (416).

The systematic literature review revealed multiple other points of seeking healthcare among patients with CH including ENT specialists, psychiatrists, surgeons, pain specialists, allergists, anaesthesiologists and alternative therapists. Neurologists were consulted late in the

diagnostic journey, most of the time due to patients' pressures to be referred, according to the qualitative data. This is in line with previous research that showed that referral for headache is often the result of patient pressure interacting with GP characteristics, service availability and organisational factors (417). Other interviewees consulted private neurologists in order to obtain a timely consultation and to avoid delays to access secondary care. Findings from both the systematic literature and interview study, emphasised GPs' important role as gatekeepers, in recognising CH and referring to secondary care for confirmation of diagnosis (226).

Table 6.2. Point of seeking healthcare

	Systematic literature review	**Qualitative study**
Point of seeking healthcare	GP (13, 41, 42, 51) ENT specialist (13, 41, 42, 51, 54) Dentist (41, 42, 51, 54) Optician/Ophthalmologist (13, 41, 42, 51) Neurologist (13, 41, 51) Neurosurgeon (42, 51) Psychiatrist (13, 42) Paediatrician (13, 41) A&E doctor (41) Cardiologist (41) Anaesthesiologist (41) Pain specialist (42) Alternative therapist (54) General medicine specialist (13) Orthopaedic surgeon (13) Chiropractor (13) Allergist (13)	GP Dentist A&E doctor Ophthalmologist Neurologist (public/private sector)

Increased awareness of CH among GPs is paramount due to their gatekeeping role. One important challenge is that such gatekeeping may delay a timely diagnosis and, as a consequence, delays treatment for patients suffering from uncommon conditions which present with common symptoms, such as CH (228). This, in turn, could result in referral delay, reduced quality of life and unnecessary healthcare cost (228). Significant diagnostic delays in CH and consulting multiple health professionals cause a substantial and avoidable burden on the health system (64). Other conditions such as cancer face delays in the diagnosis (399, 400) as a limitation of the gatekeeping system (228). Although the frequency of diagnostic errors was found to be low in the primary care in UK, the human cost was relatively high for half of those experiencing an error (418). Current measures of quality of care in primary care are not focused

on diagnostic delays and errors (391). Misdiagnosis can be prevented by access to GPs with special interest, which decreases the waiting time, referrals and cost (392). Furthermore, increased awareness of the clinical characteristics of CH is required among dentists, A&E doctors, ENT specialists, ophthalmologists who rarely recognise the condition.

6.2.2 Delays in diagnosis

Here, I discuss the delays in diagnosis after integrating the findings from the systematic literature review and qualitative data. I first present a section on different types of CH misdiagnosis and I continue with presenting the factors involved in diagnostic delays, including clinicians' and patients' factors. I conclude with a section on the impact of challenges with the diagnosis of CH, drawing from sociological concepts.

6.2.2.1 Types of misdiagnosis

There is clear evidence rising from the systematic literature review and interview data that patients with CH experience prolonged diagnostic journeys including multiple medical encounters, misdiagnosis and ineffective management. No biological markers are currently incorporated into the diagnostic process, according to the literature review on the pathophysiology of CH (37). To date, the current research failed to discover a reliable biological marker specific for CH that could facilitate the diagnosis and avoid the common misdiagnosis and delays in diagnosis (37). As a consequence, the diagnosis continues to be based on history taking according to the ICHD-3 criteria (1). Diagnostic challenges occur when a robust history cannot be undertaken due to time constrains or the ICHD-3 criteria is not well-known, as shown by the interview study. Therefore, lack of awareness of the clinical characteristic of CH leads to under-recognition and misdiagnosis.

The diagnostic journey of CH is delayed due to multiple visits to GPs or other specialities. The findings from the systematic literature review around the delayed diagnosis and misdiagnosis were confirmed by the interview study. Both patients' and clinicians' perceptions are that CH is under-recognised, most often misdiagnosed and inappropriately managed. Table 6.3 shows the type of CH misdiagnosis received, as found in the systematic literature review and qualitative study. According to the integrated data, migraine is the most common misdiagnosis, followed by trigeminal neuralgia and dental disease. However, as migraine is a common condition, a new clinical diagnosis of migraine was shown to be correct in 98% of cases (419). Cervical spine disease was also among misdiagnosis of CH, probably

due to radiation of pain to the cervical structures (14, 51). In other cases, the severe pain was labelled as psychiatric disease (15). Although the psychiatric comorbidities are prevalent in CH and should be addressed, the pain complaints should be managed separately, with evidence based therapies (394). Patients with CH were also misdiagnosed as having allergies, probably due to the presence of cranial autonomic symptoms and seasonal variation (57).

Patients with CH received multiple misdiagnosis, from other more common primary headaches to dental disease, sinus pathologies, and even psychiatric disorders and allergies. The fundamental reason why patients with CH are misdiagnosed is probably due to clinicians' lack of awareness of the clinical characteristics of CH.

Table 6.3. Types of CH misdiagnoses

	Systematic literature review	Qualitative study
Types of misdiagnosis	Migraine (14, 15, 41, 51, 57, 77) Trigeminal neuralgia (14, 15, 41, 51) Dental or jaw disease (14, 15, 41, 51, 57, 77) Sinusitis (14, 16, 41, 51, 57, 77) TTH (14, 16, 41) Ophthalmic disease (14, 51) Cervical spine disease (51) Depression (41) Idiopathic intracranial hypertension (41) Psychiatric disease (15) SUNCT(15) Allergy (57) Neck/back disease (14)	Migraine Trigeminal neuralgia Dental disease Ingrown eyelash Ear infection Glaucoma

6.2.2.2 Factors involved in delays

Both the systematic literature review and interview study identified clinicians' and patients' delay (see Table 6.4). Clinicians' delay constitutes an important factor in prolonged diagnosis. The qualitative data suggests that clinicians often do not prioritise headache conditions as they are regarded as benign. Low prevalence and lack of awareness of CH could contribute to delayed diagnosis, although misdiagnosis frequently extends to other common primary headaches such as migraine (401). The qualitative data suggests other contributing factors to missed and delayed diagnosis including confusion between the terminology 'cluster headache' and 'cluster migraine', which further supports the poor awareness of CH among first line doctors. Neurologists pointed at the poor history taken by some GPs although they

acknowledge the time restrictions for consultation. Furthermore, some GPs do not feel confident in making a diagnosis and guidelines are not always used to make a diagnosis. In addition, some clinicians found the NICE guidance difficult to use due to its length. Moreover, the complex classification of IHCD-3 might not be feasible for use in clinical practice in primary care (1). The British Association for the Study of Headache (BASH) guidelines could be an alternative to the NICE guidance and ICHD classification for the diagnosis and management of primary headaches in primary care (420).

As stated in the section 6.2.3.1, both the systematic literature review and qualitative data revealed migraine as the most common misdiagnosis. Furthermore, patients' perceptions of their diagnosis before seeking healthcare was also migraine in many cases. Some patients had a relative suffering with migraine which made them think of this diagnosis. Many diagnostic journeys of CH started with a misdiagnosis of migraine. Overlapping features of CH and migraine such as the presence of aura (421), cranial autonomic symptoms (169), the presence of triggers (alcohol, sleep) (238, 422), photophobia, phonophobia, nausea, vomiting (51, 54) might have misled the clinician to think of migraine. The current evidence does not clarify the exact role of the migraine-like symptoms in the diagnosis of CH (14, 17, 51, 54, 59, 61). Although the presence of nausea and vomiting during the attacks (54) and aggravation by physical activity (51) delayed the diagnosis of CH, other migrainous symptoms such as the presence of photophobia and phonophobia did not influence the delays (51, 54). Furthermore, the presence of aura found in 7% of patients with CH might contribute to a misdiagnosis of migraine (421). Although many primary headache disorders have associated cranial autonomic features, the intensity and frequency are more prominent in CH (169). Therefore, CH with accompanying migraine-like symptoms is a recognised clinical entity and their presence should not exclude a diagnosis of CH (61).

The systematic literature review does not elucidate the role of pain radiating to the jaw or teeth in delaying diagnosis. The jaw location of pain delayed the diagnosis in one study (51), but the pain radiating to the jaw, cheek and teeth location of pain did not have an effect on delays according to other reports (51, 54). Despite this, according to the qualitative data, patients with onset of CH after teeth extraction or pain radiating to the teeth or jaw first presented to their dentist who did not recognise the condition, therefore delaying the diagnosis. Dentists should be aware of the dental presentation of CH and onset of CH after dental treatment in order to avoid unnecessary delays and procedures (413, 414).

The episodic phenotype of CH constitutes another factor involved in delays, probably due to the presence of remission periods (54), according to the qualitative data. Some

interviewees put off seeing a doctor when the pain remitted. However, the systematic literature review does not clarify if patients with episodic CH experience delays in diagnosis more than patients with chronic CH. One study included in the systematic literature review showed that patients with episodic CH experience longer delays than chronic CH (54), but other study found the opposite (53). However, patients with chronic CH consulted on average more clinicians than patients with episodic CH (four versus two). (51). Both interviewees with episodic and chronic CH in the qualitative study experienced delays longer than 10 years. Furthermore, according to the systematic literature review, it is not clear how gender influences the delays. There was no difference in the number of clinicians seen by women with CH compared to men (42, 51), although the time to diagnosis was longer for women (51). Yet, a more recent study from 2017, showed than men wait longer than women to obtain correct diagnosis. However, the current evidence shows that both men and women are likely to delay seeing a doctor when they do not consider that symptoms require urgent attention (423).

Several other clinical characteristics were found to contribute to the diagnostic delays. Alternating attack side (54) and side shift between bouts (51) were among the factors involved in diagnostic delays in the systematic literature review. Clinicians may have regarded the CH pain as strictly unilateral as described in the ICHD-3 criteria (1), although the presence of bilateral attacks was also described (235). Patients with lower age at onset (< 20 years of age) are more likely to be misdiagnosed (14). Doctors may have a higher suspicion of secondary headaches in patients of older age and may refer to secondary care for investigations where the diagnosis is made. The decade of CH onset (<2000) also influenced the time to correct diagnosis (51). There is a reduction in the time to correct diagnosis found in several European countries, probably due to improved awareness of the condition in the last two decades (16, 42, 51, 53). Self-diagnosis, present in both the systematic literature review and qualitative data may have led to self-referral, this way improving delays (41, 42, 51). Some interviewees with CH saw neurologists in private clinics when they could not access the public sector.

In addition to clinicians' delay, certain patients' factors account for delayed diagnosis. According to the qualitative data, patients' tendency to normalise symptoms, uncertainty about the meaning of symptoms, a lay diagnosis of migraine, dental disease or head trauma-related pain influenced the decision to seek healthcare. Furthermore, stigma of headache prevented some patients from pursuing medical advice. This is in keeping with the current literature on the stigma associated with other primary headaches such as migraine (294, 424). Social stigma was shown to be present in patients suffering from other neurological conditions such as

epilepsy (424). Data from this doctoral research shows that stigma of headache extends among patients suffering with CH.

Table 6.4. Factors involved in diagnostic delays

Factors involved in diagnostic delays	**Systematic literature review**	**Qualitative study**
Clinicians' factors		
Factors with statistical significance (p<0.05)	Decade of onset <2000 (51) Episodic CH (54) Lower age at onset (14) Side shift between bouts (51) Jaw location of pain (51) Aggravation by physical activity (51) Nausea during the attacks (54) Vomiting during the attacks (54) Nocturnal onset of the attacks (54) Pain that does not reach the maximum intensity in the first five minutes (14) Alternating attack side (54)	The confusion between the terms 'cluster headache' and 'cluster migraine' Poor history taken by some clinicians Lack of confidence in making a diagnosis among some clinicians The lack of using guidelines in making a diagnosis among some clinicians Short consultation time in primary care
Factors without statistical significance (p>0.05)	Cheek location of pain (51) Lower teeth location of pain (51) Ear location of pain (51) Photophobia (51, 54) Phonophobia (54) Forehead and facial sweating (51) Absence of autonomic features (51) Interictal headache (54) Circadian rhythm (54) Restlessness (54) Pain radiating to the jaw (54)	
Patients' factors		
	Remission periods (54)	Stigma of headache Uncertainty about the meaning of symptoms Tendency to normalise symptoms Remission periods Lay diagnosis of migraine, dental disease, head trauma related pain

6.2.2.3 Impact of challenges in diagnostic journey

Prolonged diagnostic journey of CH has a negative impact on social life, work and mental health, as emerged from the CHIPS data (40). There was consensus among all interviewees, GPs and neurologists, that CH has a significant impact on employment (40). Interviewees gave examples of how their colleagues and employers often do not grasp the severity of the condition (40). Particular emphasis was given by several participants on the night attacks' impact on attention, concentration and the overall function at work. According to clinicians, patients with CH are more likely to suffer from psychiatric comorbidities such as depression, self-harm and suicidality (40). The interviewees felt that health professionals should be aware of these comorbidities and recommend appropriate medical support (40). The findings from the CHIPS study are in line with the current literature on the impact of CH on mental health (374), work and social life (225). CH is commonly referred to as 'suicide headache', as 64% of patients have passive suicidal ideation (374). Patients with CH experience difficulties at work and often require sick leave (225).

Drawing from the sociological concepts, I theorised the social impact of undiagnosed CH. According to the qualitative data, patients with CH deal with uncertainty of diagnosis for years or even decades. The lack of diagnosis can have significant impact on self-perception, identity and how others view the sufferer (338). The diagnosis, a label that legitimises the illness is often missed in patients with CH, as shown by both the qualitative data and systematic literature review (338). A lack of diagnosis leads to biographical disruption and has impact on individual's daily life and sense of self (356). Patients with CH often find themselves in a diagnostic limbo, having to deal with the uncertainty of unexplained symptoms and lack of appropriate management (334). As shown by the sociological literature, recurrent illnesses and occurrence in young individuals can lead to biographical disruption (351). Considering the episodic pattern of most cases of CH (5) and young age of onset (396), one can envisage CH as being highly disruptive. Furthermore, biographical disruption could be present in patients with CH due to the associated psychiatric comorbidity such as suicidal ideation and attempt which leads to significant emotional distress and need for urgent medical intervention (374). Our qualitative data suggests that multiple medical visits, repeated misdiagnosis and lack of effective treatment had a negative effect on the doctor-patient relationship. Self-diagnosis and the access to digital medical knowledge reshapes the lay person-doctor interaction (348).

It is now generally accepted that the disease is a result of the interaction between biological, psychological and social factors (358). Many authors support the utility of the

biopsychosocial model in headache although it is scarcely used (366-368). Reports suggest the clinical usefulness of viewing headache from a biopsychosocial rather than a narrow biomedical perspective (369-372). As a consequence of this, I suggest the biopsychosocial model in the management of CH as opposed to the dominant biomedical approach. The biopsychosocial model was implemented with success in children with chronic daily headache and patients with migraine (369-372). Addressing the CH attack suicidality and the significant impact on the social and work life should be incorporated in the standard procedures of care (330, 374). Although the comorbid psychopathology (374) and impact on social life are well documented (225), the biopsychosocial model in CH is not yet implemented.

6.2.3 Obtaining correct diagnosis

Here, I first present a section on clinicians' and patients' perception on diagnosis. I continue with a section on existing tools used to aid the diagnosis of CH, comparing their performance with the screening tool developed in this doctoral project.

6.2.3.1 Clinicians' and patients' perception on diagnosis

The 26 diagnostic journeys of CH in the interview study provide insight into which specialists were able to recognise CH. Patients' first impression of their diagnosis influenced their decision of seeking medical help and where to present first. Most patients in the interview study first presented to their GPs to seek medical advice. Although some GPs suggested the correct diagnosis, others misdiagnosed as migraine or trigeminal neuralgia despite multiple consultations and lack of response to regular analgesia. When faced with a CH patient, many GP interviewees did not feel confident in diagnosing CH. Patients complained of short consultation time by their GPs and felt that they are not taken seriously. It was previously acknowledged that, when necessary, GPs vary the consultation duration in the context of an overall structure of *'10 minutes per patient'* (425). As GPs try to catch up after longer consultations, some patients might get an inappropriately short consultations (425). This is detrimental to headache cases that are not usually prioritised as they are considered benign illnesses, as emerged from the qualitative data. GPs mentioned to rarely refer headache patients to the neurology departments in secondary care (40). In other cases, even if GPs felt confident in making a diagnosis, referrals were made as certain treatments can be initiated only in secondary care (e.g. verapamil, lithium) (40). Reassurance, anxiety and pressures from patients

to see a specialist are other reasons as to why patients are referred to secondary care (40, 417). Furthermore, referrals are not related to the clinical severity of headache, but is associated with patients' anxiety and concern and higher consultation frequency (426). Due to their role as gatekeepers, GPs play an important part in preventing the diagnostic delays of CH by selecting which patients are referred to secondary care for diagnosis and management (227). Subsequently, patients that are not recognised in primary care do not have access to specialised management. Previous study implied that the time constrains for GPs could be explained by dealing with more complex and chronic cases and a growing elderly population (427).

According to both the systematic literature review and interview study, most of the patients were diagnosed by a neurologist in the public or private sector. Self-diagnosis and self-referral prevented delays in diagnosis and facilitated timely diagnosis in some cases. However, one neurologist in the qualitative data could not recognise CH. This is in keeping with data from the systematic review that showed that neurologists occasionally missed the diagnosis (51). One GP interviewee, as well as a neurologist felt that his colleagues offer less time to headache consultations compared to other conditions. Their perception is that headache medicine is neglected by both clinicians and researchers.

Upon receiving the diagnosis, some patients were unsatisfied by the current terminology 'cluster headache'. In their opinion, the current terminology does not accurately reflect the severity and disability of this condition. As the qualitative study showed, CH interviewees did not feel understood by their employers (40). I support patients views by which 'cluster headache' might not be the appropriate terminology for the condition. I advocate that the individual should feel that the diagnosis reflects the disease experience and legitimise the suffering in order to feel accepted and understood by society. Furthermore, timely diagnosis is paramount due to the significant psychiatric comorbidity (394) and impact on social and work life (330).

6.2.3.2 Assessing the value of screening tools for CH

Despite CH's well-defined clinical characteristics, the time to correct diagnosis varies from 2.6 to nine years (42, 53). The qualitative data supports the prolonged diagnostic journey of CH, which lasted up to 39 years, in one case. In order to prevent the common misdiagnosis of CH, I developed and assessed a screening tool with images depicting headache pain to aid the diagnosis. The strength of this tool lies in its design. The tool is comprised of four main parts: images depicting headache pain, a pain scale, key descriptors of pain and key questions. This

allows a more comprehensive headache assessment using a questionnaire as a screening tool for CH. When using the total tool score as predictor (>25/32), the tool proved to have a high performance in screening for CH (sensitivity 86.4%, specificity 92%). The novelty of this tool consists in images depicting headache pain. However, images included in this tool do not clearly differentiate between CH and migraine, despite illustrating different pain intensities. Although the severity of pain is a key clinical feature of CH (1), the pain intensity is not a good discriminator from migraine in this study conducted in a tertiary headache centre. This could be related to the disease disability that influences pain reporting (298).

Several tools based on the ICHD-3b criteria have been previously developed for the screening of CH (257-263). These studies are summarised and discussed in chapter 4, section 4.2.3. Some studies also looked at the best clinical indicators for CH (257, 258, 262) (see Table 6.5). Untreated attack duration (≤ three hours) showed to be the best test-item to differentiate between CH and migraine, according to the quantitative data. This is a limitation of strictly applying the ICHD-3 criteria (1), but sometimes the attacks can last longer (257). One study that enrolled patients with attacks longer than three hours recorded a lower specificity (90%) compared to the quantitative data in this doctoral research (100%) (257). The presence of ipsilateral cranial autonomic features, which are characteristic for CH (169), recorded a low specificity (57%) in the quantitative data. When the ipsilateral cranial autonomic features were part of a previously developed three-item tool along with untreated attack duration < 180 min and strictly unilateral pain, the specificity was high (100%) (258). However, the reliability of this results is questionable as this study included a small sample size of 39 patients with CH (258). Pain described as 'excruciating agony' was present in many patients with migraine, therefore it is not a good clinical indicator of CH. This is consistent with previous data, that showed that '*excruciating pain'* is not specific for CH (specificity 34%) (257). Similarly, the data for the presence of restlessness during the attacks varies between studies, making this an unreliable clinical indicator for CH (224, 257, 312, 313).

According to this doctoral research, there is no single clinical feature that could differentiate CH from migraine. A tool capturing key clinical characteristics of CH could aid the diagnosis.

Table 6.5. Clinical indicators of CH

Quantitative study					**Wilbrink et al. 2013** (262)	**Dousset et al. 2009** (258)	**Torelli et al. 2005** (257)		
Test item									
	Untreated attack duration (≤ three hours)	Ipsilateral cranial autonomic symptoms	Excruciating agony	Restlessness	Untreated attack duration 15-180 min Attack free period (four months-three years) Male gender	Untreated attack duration < 180 min Strictly unilateral pain Ipsilateral conjunctival injection, and/or lacrimation	Short duration of attacks (three-four hours)	Excruciating pain	Restlessness
Performance									
Sensitivity	100	96	93	90	53.8*	78.4*	100	100	90
Specificity	100	57	33	56	88.9*	100*	90.2	34.1	92.7
PPV	100	46	34	44	95.5*	100*	88.2	52.6	90
NPV	100	98	92	94	30.8*	88.1*	100	100	92.7

Abbreviations: PPV: positive predictive value; NPV: negative predictive value; *aggregate performance of multiple items

6.3 Implications for clinical practice

This doctoral research has shown that it is paramount that GPs are familiar with CH and understand the clinical differences with more common headache disorders, such as migraine and TTH. GPs who are not experienced with or aware of CH, should, as a minimum, be able to recognise when dealing with a distinct syndrome and further refer to secondary care (240). The analysis of the qualitative data showed that patients with CH feel they are not 'heard' or feel they are not taken seriously. In the absence of biological markers to aid a timely and correct diagnosis, a careful history with a focus on typical features of CH is key. CH should be suspected in case of short-lasting headache (up to three-four hours), associated with prominent cranial autonomic symptoms, restlessness, circadian and circannual periodicity (1). Further referral to secondary care should be considered for confirmation of diagnosis. As shown in my doctoral research most patients have researched their symptoms and often self-diagnosed before receiving a diagnosis from a healthcare professional. Management with abortive medication should be initiated while waiting for the consultation in secondary care.

Evidence-based treatments to abort attacks (e.g., sumatriptan/zolmitriptan nasal spray or sumatriptan subcutaneous injections) should be considered in primary care (373). According to the participants in the CHIPS study, injectable triptans are expensive and the cost of medication was one of the reasons for tensions between primary and secondary care in the UK (40). Although nasal or injectable triptans are recommended due to stronger evidence, their colleagues in primary care occasionally prescribed the cheaper oral triptans (40). Some GPs are willing to prescribe the more expensive treatment when there is a clear recommendation from the neurologists. Where possible, GPs should consider prescribing high flow oxygen as abortive therapy. This is particularly useful for patients that have contraindications to triptans, and also for patients that have to limit their use of triptans to due experiencing multiple attacks per day (21). As suggested by the CHIPS data, prescribing oxygen for patients with CH was perceived as challenging by both GPs and neurologists as they were often not aware of prescription practices (40). Some GPs were not aware that oxygen was recommended as abortive medication for CH (40). Most GPs who knew about this were often not familiar with the prescription policies (40). Although in some cases neurologists or GPs were able to arrange oxygen, in other cases they were not aware of the procedure and the responsibility of oxygen prescription was passed on.

The significant impact of CH on mental health, social life and employment are well documented in the literature (225, 374). The CHIPS study supports these findings whereby patients with CH suffer with psychiatric comorbidities, have difficulties in social-activity participation and struggle to remain in employment (40). Clinicians, including GPs, should consider referral to psychiatric services when necessary. More tailored training programmes for GPs could improve patients' outcome by preventing delays in diagnosis and misuse of resources. It was previously emphasised that training should not only target the individual, but also focus on organisational issues (428).

Below, I present summary points of CH to recognise and offer first aid treatment in primary care:

- CH is a severe, unilateral, orbital, supraorbital and/or temporal short-lasting headache.
- CH is typically associated with prominent cranial autonomic symptoms and restlessness behaviour.
- The attacks usually last between 15 minutes and three hours. Patients can suffer up to eight attacks per day.
- Patients will often describe the pain like a 'red hot poker in the eye'.
- Circadian and circannual periodicity characterises CH.
- Migraine/TTH and CH can coexist.
- CH has a significant impact on mental health and employment.
- The abortive therapy of CH consists of sumatriptan/zolmitriptan nasal spray or sumatriptan subcutaneous injections. The oral triptans are not efficacious in CH.
- High flow oxygen is effective during CH attacks.
- Oral analgesia and opioids should be avoided in managing CH attacks.
- If CH is suspected, best to refer to neurology services for confirmation of diagnosis.

Here, I suggest five questions guiding the history taking to aid the recognition of CH in primary care. The ICHD-3 criteria and the test-items with the highest sensitivity and specificity in detecting CH in the quantitative study were used in designing these questions:

- Is the pain located in the orbital, supraorbital and/or temporal area?
- Are the headaches located just on one side?
- How long does the pain last for (when untreated)?
- Is the pain associated with red eyes/watery eyes/runny nose/nasal blockage/droopy eye/facial sweating?

- Do you rock back and forth, pace the floor or even bang your head against the wall during an attack?

6.4 Personal reflection

My doctoral journey started four years ago with a project on developing a screening tool for CH for a Master's degree. Soon after starting the project, I saw the potential of my research and being supported by my supervision team, I have developed this into a doctoral degree. I was pleased to see how my project grew and gained substance. As a clinician, this doctoral experience was a great opportunity to gain different qualitative and quantitative research skills and to study CH in-depth. Having met many patients with CH through this doctoral project, I feel that I have a profound understanding of their pain experience and day-to-day struggle. Being a member of the CHIPS team and undertaking qualitative research was a unique experience. I now have a deeper understanding of patients' perspectives, experiences and expectations. It has also improved my comprehension of their social and psychological context. As a clinician, it was valuable to learn about the challenges in diagnosing CH from both aspects of care: primary and secondary care. During this doctoral project I gained a range of research experiences and it also improved my clinical skills and strengthened my conviction of pursuing a career in headache medicine.

The perception drawn from my clinical experience is that other neurological conditions are better diagnosed and managed than CH. I feel that conditions such as multiple sclerosis and Parkinson's disease benefit from a higher awareness amongst patients and healthcare professionals compared to CH, despite similar prevalence (387, 388, 429). From my clinical practice, I noticed more referrals to secondary care to confirm a diagnosis of multiple sclerosis or Parkinson's disease compared to suspected cases of CH. The cause why these two neurological conditions are more recognised is unknown. My personal perception is that this is related to neglect and stigma of headache disorders, that only recently started to be recognised in the scientific literature (294, 424). Furthermore, I think that the stigma extends to clinicians specialised in headache. My view is supported by the findings from the qualitative data that showed less interest in headache medicine among neurologists and researchers. I feel that the general perception around headaches, including both the sufferers and clinicians with interest in headache should change. More attention to this field could lead to more clinicians

specialised in headache, a better diagnosis and management skills and increased awareness of headache disorders.

6.5 Future work

This doctoral project was the first step in the validation of a screening tool for patients with CH recruited from a tertiary headache clinic, after they received their diagnosis of CH or migraine. Future work could focus on the development of a more refined screening tool and its validation in primary care. As the images in the current tool did not clearly differentiate between CH and migraine, one could develop and assess images with different artistic characteristics. I would also like to explore through further qualitative study the reasons why patients had preference for certain images. This could provide insight into how they perceived the images so we could develop a better visual tool in differentiating primary headaches. I would like to know why the intensity of pain is not a good discriminator between CH and migraine. This could be due to highly disabling headache population presenting in a tertiary headache clinic. Future research should explore if the pain intensity of primary headaches correlates with the disease burden and the presence of comorbidities such as depression or anxiety. Furthermore, future work should further investigate differences in the pain intensity and pain description reported in a questionnaire study versus the pain characteristics from an interview study. In addition, exploring the pain perception in patients that suffer from both CH and migraine could give insight into the differences in severity between the two conditions.

This doctoral project informed on the challenges in the diagnosis of CH and possible factors involved in diagnostic delays and misdiagnosis. As migraine is more prevalent in women, I would like to explore, through further research if their diagnostic journey is different and if they are misdiagnosed more than men. The research should also focus on trigeminal neuralgia, a common misdiagnosis of CH, to explore if it benefits from higher awareness amongst first line doctors, despite lower prevalence (62). Although clinicians had a greater impact on the diagnostic delays and misdiagnosis, patients' factors were also present. I would like to continue the work of my doctoral project by exploring in future research why some patients delay consulting a doctor. Future research could concentrate on patients' factors such as stigma of headache, tendency to normalise symptoms, lack of awareness or uncertainty about the meaning of symptoms. I would further investigate why patients with headaches feel stigmatised and how the stigma manifests. I would extend this, through qualitative research, by exploring the stigma among clinicians with interest in headache, their perceptions on how

the headache medicine is viewed by their colleagues and how they cope with stigma. One could also investigate in future work why few clinicians and researchers pursue headache medicine. There may be a misconception that headache disorders do not represent a serious illness or that this field is not intellectually motivating. Interest could be instilled in the next generations of doctors by including more headache related education in medical school and encouraging more education during post-graduate training.

Although CH is not rare, data from this doctoral project clearly shows that a timely diagnosis is usually an exception rather than the rule. The lack of awareness of CH amongst first line clinicians, GPs and emergency doctors could be addressed with educational sessions on the diagnosis and management of CH. Increased awareness and lifting the stigma of headache could improve the lives of many sufferers.

6.6 Conclusions

CH is a severe primary headache, often unrecognised and inappropriately managed. This doctoral project examined the diagnosis of CH, through a multi-methodological approach, using both quantitative and qualitative research. Integrating data from this doctoral study, I showed that patients with CH suffer long delays in diagnosis, consult several clinicians, many receive multiple diagnosis and undergo unnecessary procedures before being correctly diagnosed. Multiple factors are involved in the diagnostic delays, including both clinicians' and patients' factors. Prolonged diagnostic journey of CH has significant impact on social life, mental health and employment. In the absence of biological markers, a screening tool for CH could aid the diagnosis. A novel 12-item screening tool with images depicting headache pain showed to have a high performance in detecting CH (sensitivity 84.6%, specificity 92%). Raising awareness of CH and making efforts in lifting the stigma of headache could smoothen the diagnostic journey of one of the most severe pain conditions.

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APPENDICES

Appendix 1

Databases and search criteria to identify articles on delays in diagnosis and misdiagnosis of CH

Database	Search term	Results
1.EMBASE	(((cluster ADJ5 headache*).ti,ab OR (cluster - like ADJ5 headache*).ti,ab OR exp "CLUSTER HEADACHE"/) AND ((misdiagnos*).ti,ab OR (diagnos* ADJ5 error*).ti,ab OR (hid* ADJ5 diagnos*).ti,ab OR (unrecognis* ADJ5 diagnos*).ti,ab OR (alternat* ADJ5 diagnos*).ti,ab OR (undiagnos*).ti,ab OR (diagnos* ADJ5 mistake*).ti,ab OR (miss* ADJ5 diagnos*).ti,ab OR exp "MEDICAL ERROR"/ OR exp "DIAGNOSTIC ERROR"/)) OR (((cluster ADJ5 headache*).ti,ab OR (cluster - like ADJ5 headache*).ti,ab OR exp "CLUSTER HEADACHE"/) AND ((delay* ADJ5 diagnos*).ti,ab OR (late ADJ5 diagnos*).ti,ab OR exp "DELAYED DIAGNOSIS"/))	138
2. PubMed	(((cluster ADJ5 headache*).ti,ab OR (cluster - like ADJ5 headache*).ti,ab) AND ((misdiagnos*).ti,ab OR (diagnos* ADJ5 error*).ti,ab OR (hid* ADJ5 diagnos*).ti,ab OR (unrecognis* ADJ5 diagnos*).ti,ab OR (alternat* ADJ5 diagnos*).ti,ab OR (undiagnos*).ti,ab OR (diagnos* ADJ5 mistake*).ti,ab OR (miss* ADJ5 diagnos*).ti,ab)) OR (((cluster ADJ5 headache*).ti,ab OR (cluster - like ADJ5 headache*).ti,ab) AND ((delay* ADJ5 diagnos*).ti,ab OR (late ADJ5 diagnos*).ti,ab))	104
3. Medline	(((cluster ADJ5 headache*).ti,ab OR (cluster - like ADJ5 headache*).ti,ab OR exp "CLUSTER HEADACHE"/) AND ((misdiagnos*).ti,ab OR (diagnos* ADJ5 error*).ti,ab OR (hid* ADJ5 diagnos*).ti,ab OR (unrecognis* ADJ5 diagnos*).ti,ab OR (alternat* ADJ5 diagnos*).ti,ab OR (undiagnos*).ti,ab OR (diagnos* ADJ5 mistake*).ti,ab OR (miss* ADJ5 diagnos*).ti,ab OR exp "MEDICAL ERRORS"/ OR exp "DIAGNOSTIC ERRORS"/)) OR (((cluster ADJ5 headache*).ti,ab OR (cluster - like ADJ5 headache*).ti,ab OR exp "CLUSTER HEADACHE"/) AND ((delay* ADJ5 diagnos*).ti,ab OR (late ADJ5 diagnos*).ti,ab OR exp "DELAYED DIAGNOSIS"/))	67
4. PsychINFO	(((cluster ADJ5 headache*).ti,ab OR (cluster - like ADJ5 headache*).ti,ab) AND ((misdiagnos*).ti,ab OR (diagnos* ADJ5 error*).ti,ab OR (hid* ADJ5 diagnos*).ti,ab OR (unrecognis* ADJ5 diagnos*).ti,ab OR (alternat* ADJ5 diagnos*).ti,ab OR (undiagnos*).ti,ab OR (diagnos* ADJ5 mistake*).ti,ab OR (miss* ADJ5 diagnos*).ti,ab)) OR (((cluster ADJ5 headache*).ti,ab OR (cluster - like ADJ5 headache*).ti,ab) AND ((delay* ADJ5 diagnos*).ti,ab OR (late ADJ5 diagnos*).ti,ab))	20
5. CINAHL	(((cluster ADJ5 headache*).ti,ab OR (cluster - like ADJ5 headache*).ti,ab OR exp "CLUSTER HEADACHE"/) AND ((misdiagnos*).ti,ab OR (diagnos* ADJ5 error*).ti,ab OR (hid* ADJ5	

	diagnos*).ti,ab OR (unrecognis* ADJ5 diagnos*).ti,ab OR (alternat* ADJ5 diagnos*).ti,ab OR (undiagnos*).ti,ab OR (diagnos* ADJ5 mistake*).ti,ab OR (miss* ADJ5 diagnos*).ti,ab OR (delay* ADJ5 diagnos*).ti,ab OR exp "DIAGNOSTIC ERRORS"/)) OR (((cluster ADJ5 headache*).ti,ab OR (cluster - like ADJ5 headache*).ti,ab OR exp "CLUSTER HEADACHE"/) AND ((delay* ADJ5 diagnos*).ti,ab OR (late ADJ5 diagnos*).ti,ab OR exp "DIAGNOSIS, DELAYED"/))	20
6. HBE	(((cluster ADJ5 headache*).ti,ab OR (cluster - like ADJ5 headache*).ti,ab OR exp "CLUSTER HEADACHE"/) AND ((misdiagnos*).ti,ab OR (diagnos* ADJ5 error*).ti,ab OR (hid* ADJ5 diagnos*).ti,ab OR (unrecognis* ADJ5 diagnos*).ti,ab OR (alternat* ADJ5 diagnos*).ti,ab OR (undiagnos*).ti,ab OR (diagnos* ADJ5 mistake*).ti,ab OR (miss* ADJ5 diagnos*).ti,ab OR exp "DIAGNOSTIC ERRORS"/)) OR (((cluster ADJ5 headache*).ti,ab OR (cluster - like ADJ5 headache*).ti,ab OR exp "CLUSTER HEADACHE"/) AND ((delay* ADJ5 diagnos*).ti,ab OR (late ADJ5 diagnos*).ti,ab))	1
7. BNI	(((cluster ADJ5 headache*).ti,ab OR (cluster - like ADJ5 headache*).ti,ab) AND ((misdiagnos*).ti,ab OR (diagnos* ADJ5 error*).ti,ab OR (hid* ADJ5 diagnos*).ti,ab OR (unrecognis* ADJ5 diagnos*).ti,ab OR (alternat* ADJ5 diagnos*).ti,ab OR (undiagnos*).ti,ab OR (diagnos* ADJ5 mistake*).ti,ab OR (miss* ADJ5 diagnos*).ti,ab)) OR (((cluster ADJ5 headache*).ti,ab OR (cluster - like ADJ5 headache*).ti,ab) AND ((delay* ADJ5 diagnos*).ti,ab OR (late ADJ5 diagnos*).ti,ab))	1
8. AMED	(((cluster ADJ5 headache*).ti,ab OR (cluster - like ADJ5 headache*).ti,ab) AND ((misdiagnos*).ti,ab OR (diagnos* ADJ5 error*).ti,ab OR (hid* ADJ5 diagnos*).ti,ab OR (unrecognis* ADJ5 diagnos*).ti,ab OR (alternat* ADJ5 diagnos*).ti,ab OR (undiagnos*).ti,ab OR (diagnos* ADJ5 mistake*).ti,ab OR (miss* ADJ5 diagnos*).ti,ab)) OR (((cluster ADJ5 headache*).ti,ab OR (cluster - like ADJ5 headache*).ti,ab) AND ((delay* ADJ5 diagnos*).ti,ab OR (late ADJ5 diagnos*).ti,ab))	0
9. HMIC	(((cluster ADJ5 headache*).ti,ab OR (cluster - like ADJ5 headache*).ti,ab) AND ((misdiagnos*).ti,ab OR (diagnos* ADJ5 error*).ti,ab OR (hid* ADJ5 diagnos*).ti,ab OR (unrecognis* ADJ5 diagnos*).ti,ab OR (alternat* ADJ5 diagnos*).ti,ab OR (undiagnos*).ti,ab OR (diagnos* ADJ5 mistake*).ti,ab OR (miss* ADJ5 diagnos*).ti,ab)) OR (((cluster ADJ5 headache*).ti,ab OR (cluster - like ADJ5 headache*).ti,ab) AND ((delay* ADJ5 diagnos*).ti,ab OR (late ADJ5 diagnos*).ti,ab))	0
10.Cochrane Library	#1cluster near/5 headache*:ti,ab,kw (Word variations have been searched); #2 cluster-like headache*:ti,ab,kw (Word variations have been searched); #3 MeSH descriptor: (Cluster headache) explode all trees; #4 misdiagnos* #5 diagnos* near/5 error*; #6 hid* near/5 diagnos*; #7 unrecognis* near/5 diagnos*; #8 alternat* near/5 diagnos*; #9 undiagnos* ; #10 diagnos* near/5 mistake* ;#11 miss* near/5 diagnos* #12 MeSH descriptor: (Diagnostic error) explode all trees; #13 delay* near/5 diagnos*; #14 late near/5 diagnos*; #15 MeSH descriptor	1

	(Delayed diagnosis) explode all trees; #16 {or #1-#3}; #17 {or #4-#12}; #18 {or #13-#15}; #19 {and #16-#17}; #20 {and #16, #18}; #21 {or #19-#20}	
Total number of references		352
Deduplicates removed		154
Total number of articles		**198**

Abbreviations: CINAHL: Cumulative Index to Nursing and Allied Health Literature; BNI: British Nursing Index; HMIC: Health Management Information Consortium; AMED: Allied and Complementary Medicine Database; HBE: Health Business Elite

Appendix 2

The Joanna Briggs Institute (JBI) Critical Appraisal tool for case series

JBI Critical Appraisal Checklist for Case Series

Reviewer_____Date_____

Author _____Year_____Record Number_____.

	Yes	No	Unclear	Not applicable
1. Were there clear criteria for inclusion in the case series?	☐	☐	☐	☐
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	☐	☐	☐	☐
3. Were valid methods used for identification of the condition for all participants included in the case series?	☐	☐	☐	☐
4. Did the case series have consecutive inclusion of participants?	☐	☐	☐	☐
5. Did the case series have complete inclusion of participants?	☐	☐	☐	☐
6. Was there clear reporting of the demographics of the participants in the study?	☐	☐	☐	☐
7. Was there clear reporting of clinical information of the participants?	☐	☐	☐	☐
8. Were the outcomes or follow up results of cases clearly reported?	☐	☐	☐	☐
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	☐	☐	☐	☐
10. Was statistical analysis appropriate?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

_____

_____

_____

Appendix 3

Oxford Centre for Evidence Based Medicine (OCEBM) Critical Appraisal of Survey studies

CEBMa center for Evidence-Based Management

Critical Appraisal of a Survey

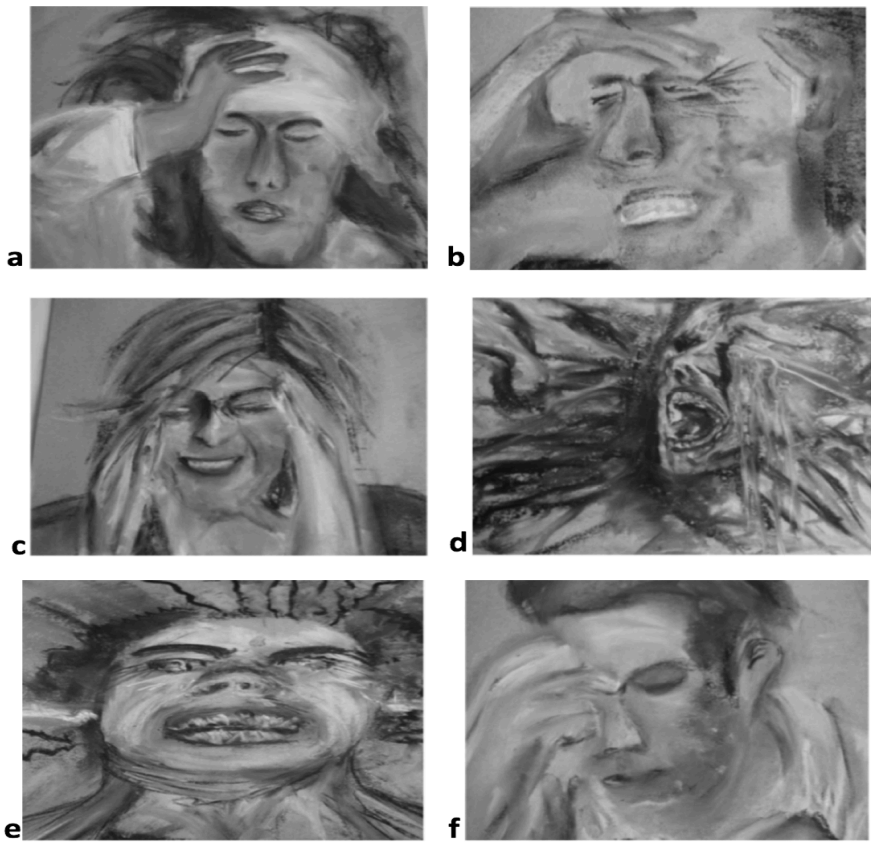
Appraisal questions	Yes	Can't tell	No
1. *Did the study address a clearly focused question / issue?*			
2. *Is the research method (study design) appropriate for answering the research question?*			
3. *Is the method of selection of the subjects (employees, teams, divisions, organizations) clearly described?*			
4. *Could the way the sample was obtained introduce (selection)bias?*			
5. *Was the sample of subjects representative with regard to the population to which the findings will be referred?*			
6. *Was the sample size based on pre-study considerations of statistical power?*			
7. *Was a satisfactory response rate achieved?*			
8. *Are the measurements (questionnaires) likely to be valid and reliable?*			
9. *Was the statistical significance assessed?*			
10. *Are confidence intervals given for the main results?*			
11. *Could there be confounding factors that haven't been accounted for?*			
12. *Can the results be applied to your organization?*			

Appendix 4

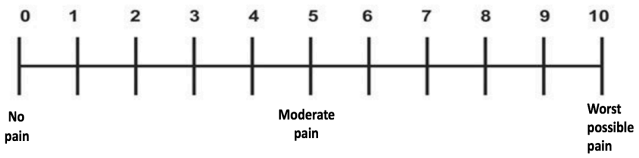
Screening tool tested on patients with migraine

Male / Female **Migraine**
Age__ **Episodic / Chronic**

1 **Please choose only ONE image that best illustrates your migraines**



2 **Please mark with an X the intensity of your migraines on the scale below**



3 Please choose only ONE option from each category that best describes your migraines

Intensity	Mild	Moderate	Severe	Very Severe	Excruciating
Nature	Pressure	Throbbing	Stabbing	Burning	Other_____
Description	Red hot poker in the eye		Pounding heart in the head		Other_____

4 Please answer the following questions

A. Do you feel restless (pace the floor or rock your body) most of the time during your migraines?

YES NO

B. When you have a migraine is the pain 'excruciating agony' most of the time?

YES NO

C. Do your migraines come at specific times?

YES NO

D. Are your migraines located just on one side?

YES NO

E. Are there any associated symptoms (one or more of the following: red eyes, watery eyes, droopy eye, runny nose, facial sweating, fullness in the ear) on the same side as the pain?

YES NO

F. How long does a migraine last for?

With medication ____ Without medication____

List of abbreviations

CH: Cluster headache

ECH: Episodic cluster headache

CCH: Chronic cluster headache

CM: Chronic migraine

EM: Episodic migraine

TACs: Trigeminal autonomic cephalalgias

TTH: Tension-type headache

ICHD: International Classification of Headache Disorders

CHIPS: Cluster Headache: Impact and Perception Study

PRISMA: Preferred reporting items for systematic review and meta-analysis

OCEBM: Oxford Centre for Evidence Based Medicine

JBI: Joanna Briggs Institute

ENT: Ear nose and throat

SUNCT: Short lasting neuralgiform headache with conjunctival injection and tearing

GP: General practitioner

CINAHL - Cumulative Index to Nursing and Allied Health Literature

BNI – British Nursing Index

HMIC - Health Management Information Consortium

AMED - Allied and Complementary Medicine Database

HBE – Health Business Elite

GM: Grey matter

WM: White matter

sMRI: Structural magnetic resonance imaging

T1w: T1 weighted magnetic resonance imaging

RBF: Cerebral blood flow

DTI: Diffusion tensor imaging

FA: Fractional anisotropy

VBM: Voxel-based morphometry

TBSS: Tract-based spatial statistics

ROI: Region of interest

rCBF: Regional cerebral blood flow

SPECT: Single-photon emission computer tomography

VBA: Voxel-based analysis

ACC: Anterior cingulate cortex

ICA: Internal carotid artery

PET: Positron emission tomography

FDG-PET: Fluorodeoxyglucose-positron emission tomography

ICA: Independent component analysis

SB-FCA: Seed-based functional connectivity analysis

FC: Functional connectivity

SN: Salience networks

IH-MRS: In vivo magnetic resonance spectroscopy

31P-MRS: Phosphorus magnetic resonance spectroscopy

ATP: Adenosine triphosphate

ADP: Adenosine diphosphate

MRA: Magnetic resonance angiography

DW-MRI: Diffusion weighted- magnetic resonance imaging

DBS: Deep brain stimulation

ONS: Occipital nerve stimulation

RS-fMRI: Resting state functional magnetic resonance imaging

TCC: Trigeminocervical complex

SusS: superior salivatory nucleus

LC: Locus coeruleus

Ins: Insula

RS: Retrosplenial

Ect: Ectorhinal

RVM: Rostral ventromedial medulla

PtA: Parietal association area

Au: Auditory association area

TG: Trigeminal ganglion

SPG: Sphenopalatine ganglion

PAG: Periaqueductal grey

M1/M2: Primary and secondary motor area

S1/S2: Primary and secondary sensory areas

V1/V2: Primary and secondary visual areas

PPV: Positive predictive value

NPV: Negative predictive value

FPR: False positive rate

FNR: False negative rate

ROC: Receiver operating characteristics

SD: Standard deviation