

CLUSTER HEADACHE

DR ANISH BAHRA

The Headache Group

Institute of Neurology

University College London

London, UK

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Abstract

Cluster headache is a relatively uncommon primary head pain syndrome. In this thesis a total of 230 individuals with cluster headache were interviewed, of whom 19 underwent functional imaging with positron emission tomography (PET) to address pathophysiological mechanisms of the syndrome, and to better understand the clinical problem. Seventy-six percent were recruited through national support groups. The male to female ratio was 2.5:1. Although there were some shared clinical features with migraine the syndrome of cluster headache was clinically distinct: a strictly unilateral first division trigeminal head pain, with ipsilateral autonomic features and a characteristic circadian periodicity to short-lived attacks and bouts of attacks. With presumed better access to neurologists the time to diagnosis has improved over the decades, however despite this, the management of such patients remains suboptimal.

Nine patients with chronic cluster headache were imaged with PET during a nitroglycerine induced cluster headache. First, activation was seen during pain in structures associated with the processing of pain, e.g the cingulate cortex, the thalamus and insula. Secondly there was activation of the posterior hypothalamus, a region not reported in previous PET studies of pain, and consistent with clinical and experimental studies, supporting dysfunction of the hypothalamus in cluster headache. Thirdly, there was activation of structures corresponding to the cranial vessels. The activations observed were not seen in patients imaged out of the active bout after attempted triggering of an attack was unsuccessful (n=8). In a single patient with cluster headache and migraine, triggering with nitroglycerine induced a typical migraine attack. Activation was observed in structures associated with pain processing, the dorsorostral brainstem and in the region of the cranial vessels. There was no activation in the hypothalamus. This suggests that primary head pain syndromes may be

pathophysiologically differentiated on the basis of distinct patterns of brain activation. Moreover, the term neurovascular headache more appropriately describes the syndromes of migraine and cluster headache.

Description of thesis

This thesis is divided into four parts.

Part 1 provides an introduction to cluster headache. The clinical characteristics and epidemiology of the syndrome are followed by a discussion of current hypotheses pertaining to pathophysiology, and a review of therapeutic management relevant to both the described PET studies and clinical data obtained. The final chapter of this section addresses the principles of PET and summarises functional imaging studies in the investigation of pathophysiological mechanisms in primary head pain.

Part 2 comprises of three PET studies. The first is a study of patients with chronic cluster headache imaged during an acute attack of cluster headache. Using the same study design the second is a study of individuals with episodic cluster headache imaged out of the active bout. The third is a single PET study of a patient with migraine and cluster headache imaged during the active bout of cluster headache but during an acute typical migraine headache attack.

Part 3 comprises a clinical and epidemiological study of the 230 patients who were interviewed during recruitment of suitable individuals for the three PET studies.

The studies are presented in the order in which the data was obtained and analysed during the three year term of my research.

Part 4 consists of a summary of the main findings and conclusions of the thesis.

Abbreviations

ACC	Anterior cingulate cortex
BA	Brodmann area
CGRP	Calcitonin gene related peptide
CBF	Cerebral blood flow
CSF	Cerebrospinal fluid
CCH	Chronic cluster headache
CH	Cluster headache
CHA	Cluster headache active
CHI	Cluster headache inactive
CT	Computerised tomography
DHE	Dihydroergotamine
ENT	Ear, nose and throat
EEG	Electroencephalogram
ECAT	Emission Computerised Axial Tomography
ECH	Episodic cluster headache
F	Female
FSH	Follicle stimulating hormone
FWHM	Full width half maximum
hrs	Hours
HBO	Hyperbaric oxygen
IHS	International Headache Society
LH	Luteinising hormone
LHRH	Luteinising hormone releasing hormone
MRA	Magnetic resonance angiography

M	Male
HA*	Mild generalised featureless headache post-nitroglycerine
MMPI	Minnesota multiphasic personality inventory
mins	Minutes
GTN	Nitroglycerine
PET	Positron emission tomography
REM	Rapid eye movement
rCBF	Regional cerebral blood flow
SPECT	Single photon emission computerised tomography
SPM	Statistical parametric mapping
TSH	Thyroid stimulating hormone
TRH	Thyrotropin releasing hormone
VIP	Vasoactive intestinal peptide
VAS	Visual analogue scale
yr	Year

Tables

Table 2.1	Associated features in cluster headache	34
Table 2.2	Associated features in cluster headache	34
Table 2.3	Attack duration and frequency	43
Table 2.4	Bout duration and frequency	44
Table 7.1	Number of scans for each condition of interest	124
Table 7.2	Increases in blood flow during an induced attack of acute cluster headache compared to the pain-free state	125
Table 8.1	Conditions of interest following GTN in patients with cluster headache in (CHA) and out (CHI) of the active bout	131
Table 8.2	Significant increases in blood flow in patients in (CHA) / out (CHI) of the bout during the scans defined for CH / HA* compared with rest	137
Table 9.1	Regional increases in blood flow during migraine headache compared to rest	148
Table 9.2	Regional increases in blood flow post-sumatriptan compared to rest	149
Table 10.1	Site of pain	170
Table 10.2	Side of attacks	171
Table 10.3	Autonomic features	172
Table 10.4	Additional features	173
Table 10.5	Periodicity of attacks and bouts, alcohol triggering and smoking history	174

Table 10.6	Male:Female (M:F) ratio, time to diagnosis and practitioners seen relative to year of onset of cluster headache	175
Table 10.7	Specialists seen prior to diagnosis	176
Table 10.8	Acute therapy	177
Table 10.9	Preventative therapy	178
Table 10.10	Alternative therapy	179

Figures

Figure 7.1a	Comparison of the nitroglycerine induced acute cluster headache attack and rest (no pain) conditions in nine patients with chronic cluster headache	126
Figure 7.2	Activation of structures involved in pain processing and of the intracranial vessels	127
Figure 7.3	Comparison of GTN-induced acute cluster headache attack versus rest in nine patients with chronic cluster headache – Activation of the intracranial vessels	128
Figure 7.4	Activation of the intracranial vessels (arrowed) in a single case of spontaneous cluster headache	129
Figure 9.1	Dorsorostral brainstem activation during migraine headache compared to rest	150
Figure 9.2	Cortical and subcortical activations during migraine headache compared to rest	151
Figure 9.3	Activation of the intracranial vessels during migraine headache compared to rest	152
Figure 9.4	Activation pattern of the dorsorostral brainstem and intracranial vessels in the three conditions of interest	153
Figure 10.1	Distribution of bout frequency amongst the cohort of patients studied	180
Figure 10.2	The distribution of the diagnosis of cluster headache made by neurologists by year in which the diagnosis was made	181
Figure 10.3	The distribution of diagnosed cluster headache amongst practitioners	182

Publications arising from this thesis

Bahra, A., May, A. & Goadsby, P.J. (2002). Cluster Headache : A prospective study with diagnostic implications. *Neurology*, 58 (3), 354-361

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Contents

Abstract	2
Description of thesis	4
Abbreviations	5
Tables	7
Figures	9
Publications arising from this thesis	10
Publications during research period not reported in this thesis	11
Acknowledgements	13
Contents	14

PART 1	INTRODUCTION AND BACKGROUND	21
Chapter 1	Epidemiology	22
1.1	Prevalence	22
1.2	Male:Female (M:F) ratio	22
1.3	Age of onset	24
1.4	Ethnic origin	25
1.5	Family history of cluster headache	25
1.6	History and family history of migraine	26
1.7	Patient characteristics	27
1.7.1	<i>Smoking</i>	27
1.7.2	<i>Alcohol and Triggering of attacks</i>	28
1.7.3	<i>Personality traits</i>	28
1.8	Comorbid disorders	29

1.8.1	<i>Peptic ulcer disease</i>	29
1.8.2	<i>Cardiac disease</i>	30
Chapter 2	Clinical Characteristics	32
2.1	Localisation of pain	32
2.2	Associated features	32
2.3	Duration and frequency of attacks	35
2.3.1	<i>Periodicity of attacks</i>	35
2.4	Episodic Cluster Headache - Duration and frequency of bouts of cluster headache	36
2.4.1	<i>Periodicity of bouts</i>	37
2.5	Chronic Cluster Headache	38
2.6	Differences Between Episodic and Chronic Cluster Headache	38
2.7	Symptomatic Cluster Headache	40
2.8	Post-traumatic cluster headache	41
Chapter 3	The Pathophysiology of Cluster Headache	45
3.1	The pain phenomenon	45
3.2	The autonomic phenomena	47
3.3	Pathophysiological hypotheses	50
3.3.1	<i>A pathophysiological focus in the region of the pericarotid cavernous sinus</i>	50
3.3.2	<i>Central pathophysiological mechanisms involving the hypothalamus</i>	53

3.3.3	<i>The role of the carotid body in cluster headache</i>	61
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Chapter 4	Treatment of Cluster Headache	64
4.1	Introduction	64
4.2	Acute attack treatment	64
4.2.1	<i>Subcutaneous sumatriptan</i>	64
4.2.2	<i>Intranasal sumatriptan</i>	66
4.2.3	<i>Oral Zolmitriptan</i>	67
4.2.4	<i>Oxygen Therapy</i>	68
4.2.5	<i>Ergotamine</i>	71
4.2.6	<i>Intranasal lignocaine and cocaine</i>	72
4.3	Preventative treatment	74
4.3.1	<i>Calcium channel blockers</i>	74
4.3.2	<i>Lithium</i>	76
4.3.3	<i>Corticosteroids</i>	78
4.3.4	<i>Methysergide</i>	79
4.3.5	<i>Ergotamine</i>	80
4.3.6	<i>Pizotifen</i>	81
4.3.7	<i>Sodium Valproate</i>	81
4.3.8	<i>Other prophylactic agents</i>	82
4.4	Surgical Treatment	82
4.4.1	<i>Introduction</i>	82
4.4.2	<i>Trigeminal ganglion</i>	83
4.4.3	<i>Trigeminal nerve</i>	84
4.4.4	<i>Pterygopalatine ganglion</i>	85

4.4.5	<i>Nervus Intermedius</i>	86
4.4.6	<i>Greater superficial petrosal nerve</i>	87
4.5	Summary	88
Chapter 5	Functional Imaging in Head and Facial Pain	89
5.1	Functional imaging studies in migraine headache	89
5.1.1	<i>Introduction</i>	89
5.1.2	<i>Xenon-133 with the use of stationary detectors and single photon positron emission tomography (SPECT) in migraine with aura</i>	90
5.1.3	<i>Perfusion weighted magnetic resonance imaging in migraine with aura</i>	93
5.1.4	<i>Xenon-133 and the use of stationary detectors and SPECT studies in migraine without aura</i>	94
5.1.5	<i>Positron emission tomography (PET)</i>	95
5.1.6	<i>PET in migraine with and without aura</i>	99
5.2	Functional imaging studies in cluster headache	101
5.2.1	<i>Xenon-133 with the use of stationary detectors and SPECT studies in cluster headache</i>	101
5.2.2	<i>PET studies in cluster headache</i>	104

5.3	Summary	104
PART 2	PET STUDIES OF CLUSTER HEADACHE	106
Chapter 6	Oxygen-15 Tracer Positron Emission Tomography	107
6.1	Introduction	107
6.2	Method	108
6.3	Statistical Analysis	111
6.4	Ethics Approval	115
Chapter 7	PET Study 1 - Acute Cluster Headache Attacks	116
7.1	Introduction	116
7.2	Methods	117
7.3	Results	117
7.4	Discussion	119
7.5	Summary	123
Chapter 8	PET Study 2 - Cluster Headache : A Comparison of Patients in and out of the Active Bout	130
8.1	Introduction	130
8.2	Methods	130
8.3	Results	131
8.4	Discussion	133
8.5	Summary	136

Chapter 9	PET Study 3 - Co-existent Migraine and	138
	Cluster Headache	
9.1	Introduction	138
9.2	Methods	139
9.3	Results	140
9.4	Discussion	142
9.5	Summary	146
 PART 3	 A CLINICAL STUDY OF CLUSTER	 154
	HEADACHE	
Chapter 10	Cluster Headache : A Prospective Clinical	155
	Study of 230 Patients	
10.1	Introduction	155
10.2	Methods	155
10.3	Results	156
<i>10.3.1</i>	<i>Sample Group</i>	<i>156</i>
<i>10.3.2</i>	<i>Clinical Characteristics- attacks</i>	<i>156</i>
<i>10.3.3</i>	<i>Clinical characteristics - patients</i>	<i>158</i>
<i>10.3.4</i>	<i>Cluster headache in Women</i>	<i>159</i>
<i>10.3.5</i>	<i>Accuracy and Rapidity of Diagnosis</i>	<i>160</i>
<i>10.3.6</i>	<i>Treatment Regimens</i>	<i>161</i>
10.4	Discussion	161
<i>10.4.1</i>	<i>Clinical characteristics</i>	<i>162</i>
<i>10.4.2</i>	<i>Cluster headache and women</i>	<i>163</i>
<i>10.4.3</i>	<i>Genetics, Cluster Headache and Migraine</i>	<i>165</i>
<i>10.4.4</i>	<i>Natural History of Cluster Headache</i>	<i>166</i>

10.4.5	<i>Diagnostic (in)accuracy</i>	166
10.4.6	<i>Management Strategies in Cluster Headache</i>	167
10.5	Summary	168
PART 4	CONCLUSION	183
Chapter 11	Conclusion	184
References		188

PART 1

INTRODUCTION AND BACKGROUND

CHAPTER 1

Epidemiology

1.1 Prevalence

Cluster headache is a relatively uncommon primary pain disorder. Current prevalence data are based mainly on estimates. The prevalence from a study of 18 year old Swedish army recruits was 0.09% (Ekbom *et al.*, 1978). Extrapolation of these results yielded prevalence rates in the United States of 0.4% for men and 0.08% for women (Kudrow, 1980). The most comprehensive prevalence data is from the population of the Republic of San Marino. This was based upon review of 15 year medical records and writing to each of almost 22,000 inhabitants with a resultant prevalence rate of 0.07% (D' Alessandro *et al.*, 1986).

1.2 Male:Female (M:F) ratio

Cluster headache has been more commonly reported in men than women. The observed ratio has varied between 3.2-7.1:1 (Andersson, 1985; Ekbom & Waldenlind, 1981; Klapper *et al.*, 2000; Krabbe, 1986; Kudrow, 1980; Lovshin, 1961; Manzoni, 1998). All the series but one (Manzoni, 1998) were published prior to the classification criteria established by the International Headache Society (IHS) (Headache Classification Committee of the International Headache Society, 1988). Graham described individuals with longstanding cluster headache as having 'leonine facies' and commented that the females sufferers have a masculine appearance (Graham, 1972), an observation that was subsequently supported (Kudrow, 1973). However, there is no evidence of alteration in the male nor female sex hormones to account for this observation and the difference in sex distribution. In fact low serum testosterone levels have been reported in men during the active bout compared to the remission period, and in and out of the bout compared

to control groups (Facchinetti *et al.*, 1986; Kudrow, 1976b; Kudrow, 1980; Murialdo *et al.*, 1989; Romiti *et al.*, 1983). There is little known about the contribution of female hormones in cluster headache. The onset of cluster headache in women is later than migraine (Kudrow, 1980) and unrelated to menarche (Manzoni *et al.*, 1988) (see 1.3). Menstruation does not seem to influence the symptoms (Ekbom & Waldenlind, 1981; Manzoni *et al.*, 1988). It has been reported that the majority of females notice remission during pregnancy although Manzoni *et al.* found no differences between cluster headache sufferers and controls (Manzoni *et al.*, 1988). The use of the oral contraceptive pill is not different to the general population but only anecdotal reports exist about any influences of the pill on the attacks of cluster headache. Women who develop cluster headache before having children tend to have fewer children than age-matched migraineurs, whilst in those with onset after their pregnancies the mean number of childbirths are similar to the general population. Infertility associated with the onset of the syndrome, or psychological factors have been put forward to explain this observation (Ekbom & Waldenlind, 1981; Manzoni *et al.*, 1988). Finally cluster headache can continue into the menopause or may start de novo (Ekbom & Waldenlind, 1981; Peatfield *et al.*, 1982); infact the age of onset in women shows a second peak in the 6th decade (see 1.3).

An increased incidence of past head injury has been reported in cluster headache sufferers compared to age- and sex-matched controls, and individuals with migraine, and tension-type headache (Friedman & Mikropoulos, 1958, Manzoni, 1983; Lance & Goadsby, 1998; Manzoni, 1999). It has been postulated that the male predominance may be due to a greater tendency of males to accidents (Manzoni, 1999; Manzoni *et al.*, 1983b). The most recent reported series of cluster headache sufferers (Manzoni, 1998) addressed the M:F ratio by decade of onset. A gradual reduction in the M:F ratio was

seen over time from 6.2:1 before 1960 to 2.1:1 for those individuals with onset between 1990 and 1995. This was attributed to significant changes in lifestyle, such as smoking and employment rate, which have shown a similar fall in M:F ratio for the corresponding decades.

An atypical pattern of cluster headache in women has been noted, although not validated (Lovshin, 1961; Peatfield *et al.*, 1982). This observation may be accounted for by the more recently described syndrome of paroxysmal hemicrania (Antonaci & Sjaastad, 1989). Paroxysmal hemicrania is a syndrome clinically related to cluster headache and differentiated by a female preponderance, shorter attack duration, increased daily attack frequency and an absolute response to indomethacin (Headache Classification Committee of the International Headache Society, 1988).

1.3 Age of onset

The mean age of onset of cluster headache falls between the 2nd and 4th decade, with the peak age of onset occurring between 20 and 30 (Ekbom, 1970a; Friedman & Mikropoulos, 1958; Kudrow, 1980; Manzoni, 1998; Sutherland & Eadie, 1972). However the youngest reported patient was 1 year old (Kudrow, 1980) while the oldest was 73 (Sutherland & Eadie, 1972). There does not seem to be a significant difference in mean age of onset between men and women (Ekbom, 1970a; Kudrow, 1980; Manzoni, 1998). The incidence diminishes with age and a similar pattern is seen in both men and women. Some studies have shown a bimodal distribution of age of onset in women with a second peak in the 6th decade (Ekbom, 1970a; Kudrow, 1980; Peatfield *et al.*, 1982; Rozen *et al.*, 2001). An older age of onset is seen in individuals with chronic compared to episodic cluster headache for both men and women (Kudrow, 1980, Manzoni, 1999 #1147). Few studies have had sufficient number of patients to compare

primary and secondary cluster headache. The mean age of onset of primary compared to secondary cluster headache appears to be later (Manzoni, 1999) and one study has shown the onset of primary cluster headache does not seem to diminish until the 6th decade while that of secondary cluster headache shows a bimodal pattern with an increased frequency in the 5th and 6th decades (Kudrow, 1980).

1.4 Ethnic origin

Few studies have addressed race. Cluster headache occurs in all races (Kudrow, 1980). Two studies reported cluster headache to be relatively more common in the Afro-Caribbean population particularly in the women, with a M:F ratio of 3-3.5:1 (Kudrow, 1980; Lovshin, 1961).

1.5 Family history of cluster headache

Cluster headache has not generally been thought to have a genetic predisposition. However a positive family history had been reported in 1.9-10 % of patients with cluster headache (Klapper *et al.*, 2000; Kudrow & Kudrow, 1994) and there have been occasional reports in monozygotic twins (Couturier *et al.*, 1991; Roberge *et al.*, 1992; Sjaastad *et al.*, 1993). In a study of 200 women with cluster headache, 24 (12%) were found to have at least one first-degree relative with the disorder. Three generations of cluster headache were found in 7 of 24 kindreds (29%). Parenteral cluster headache was found in 19/24 of the probands (79%); in 14/24 (74%) the transmission was from father to proband. Of the 1652 first-degree relatives of 300 male and female patients, 3.45% had cluster headache. This is 13 times the expected frequency of cluster headache in the general population (taken as 0.26%) (Kudrow & Kudrow, 1994). Notably not all relatives were interviewed and descriptions from some probands was taken as adequate. Russell and colleagues found a positive family history of cluster headache (in first- and

second-degree relatives) in 25/366 (7%) of families of 370 probands (21% women) with cluster headache (seven patients belonged to 3 families) (Russell *et al.*, 1995a). The risk of cluster headache in first- and second-degree relatives was 14 and 2 times that of the general population. This was based upon a population prevalence of 69 per 100,000 adjusted for age and sex (D' Alessandro *et al.*, 1986). Montagna and colleagues found a positive family history of cluster headache in 2.3% of first- and second-degree relatives of 222 probands (Montagna *et al.*, 1998). Leone and colleagues studied the occurrence of cluster headache in the families of 220 patients with cluster headache. Compared with the general population, first degree relatives had a 39-fold increased risk of cluster headache and second degree relatives an 8-fold increased risk (Leone *et al.*, 2001). The population prevalence was again taken as 69 per 100,000. In summary, these studies have confirmed a higher familial occurrence of cluster headache. Some families have shown a pattern compatible with autosomal dominant inheritance (D'Amico *et al.*, 1996; Montagna *et al.*, 1998; Russell *et al.*, 1995b; Spierings & Vincent, 1992). Methodological differences may explain the differences in familial risk observed in these studies.

1.6 History and family history of migraine

The reported occurrence of migraine in patients with cluster headache has varied considerably between 0 and 65% (Duvoisin *et al.*, 1961; Ekbom, 1974; Graham, 1972; Klapper *et al.*, 2000; Kudrow, 1980; Lance & Anthony, 1971; Manzoni *et al.*, 1983b; Sutherland & Eadie, 1972). The discrepancies can be attributed to a combination of different sample sizes, diagnostic criteria and method of data collection. The age of onset of cluster headache is reported to be later than for migraine and studies which have addressed the temporal relationship of the two disorders in the same individual have shown that in the majority the attacks of migraine stop following the onset of

cluster headache (Andersson, 1985; Kudrow & Kudrow, 1994; Solomon & Cappa, 1986). However the co-existence of migraine and cluster headache does occur. One report of 10 patients commented that a 'migraine crisis' did not occur during the cluster period in any patient and moreover the attacks of migraine and cluster headache did not present in close proximity to one another (D'Amico *et al.*, 1997). However other authors have witnessed occasional migraine attacks during, and often limited to, the cluster period, with migraine attacks witnessed in some male and female patients with no clear history of migraine (Kudrow & Kudrow, 1994).

Similar discrepancies exist with regard to the familial incidence of migraine in individuals with cluster headache. However most of the larger published series have reported the familial incidence of migraine in first degree relatives of individual with cluster headache to be the same as the incidence in the general population (Ekblom, 1974; Ekblom & Waldenlind, 1981; Kudrow, 1980; Manzoni *et al.*, 1983b).

1.7 Patient characteristics

1.7.1 Smoking

The majority of individuals with cluster headache have a longstanding history of smoking, current or past. Significantly more patients with cluster headache smoked cigarettes in comparison to a control group; the number of cigarettes smoked per day was also significantly greater in cluster headache sufferers than controls (Kudrow, 1980). Of a series of 370 cluster headache patients, 330 were smokers or former smokers (Manzoni, 1999). Seventy-eight percent had started smoking before the onset of cluster headache, 11% after the onset, and 11% had never smoked. Those who had stopped smoking following the onset of cluster headache continued to experience

attacks. However since the series was clinic-based this group of individual may have represented a biased sample.

1.7.2 Alcohol and Triggering of attacks

During the active bout cluster headache attacks can be precipitated by alcohol (Friedman & Mikropoulos, 1958; Krabbe *et al.*, 1984; Kudrow, 1980; Symonds, 1956) and nitroglycerine (Krabbe *et al.*, 1984). Ekbom showed a 100% success rate at triggering acute attacks during the middle of a bout with 1mg sublingual nitroglycerine (Ekbom, 1968). The attack was preceded by a relatively consistent latency period between 30-50 minutes and followed by a refractory period of a few hours. A higher frequency of severe attacks could be provoked during the middle of the bout in comparison to the end of the bout. Attacks could not be triggered when patients were out of the active bout. Triggered attacks were clinically identical to spontaneous attacks. Triggered attacks have also been shown experimentally to be identical to spontaneous attacks (Fanciullacci *et al.*, 1995; Goadsby & Edvinsson, 1994a). Although sufferers tend to avoid alcohol consumption during the active bout, a higher consumption of alcohol in cluster headache patients compared to controls has been reported (Kudrow, 1980; Manzoni, 1999).

1.7.3 Personality traits

Graham commented upon the aggressive behaviour of cluster headache sufferers during the acute attack. He also reported the upon the hypermasculine external appearance of cluster headache sufferers, but postulated the underlying personality to be ambitious and perfectionist with greater dependency needs, and inability to disclose feelings of anger, guilt and inadequacy (Graham, 1972). However this has not been borne out on formal evaluation. Kudrow and Sutkus (Kudrow & Sutkus, 1979) evaluated 41 patients

with cluster headache using the Minnesota Multiphasic Personality Inventory (MMPI) in comparison with 217 individual with other types of headache and a group of 30 controls. There was no difference between migraine and cluster headache sufferers. Although cluster headache sufferers did score higher than controls on some scales, the mean of the five MMPI scales was not different to controls. This was confirmed in a subsequent study comparing 40 cluster headache sufferers with 49 migraineurs (Cuypers *et al.*, 1981). However cluster headache sufferers did show elevated 'anxiety' scores and slightly diminished scores for 'masculinity'. It has been proposed that cluster headache sufferers are depressed. Marchesi *et al.* studied the prevalence of different types of headache in 160 depressed patients. Cluster headache was diagnosed in 1.2%, and migraine and tension-type headache in 22.5 and 24.4% respectively (Marchesi *et al.*, 1989).

1.8 Comorbid disorders

1.8.1 Peptic ulcer disease

Several investigators have reported an association between cluster headache and peptic ulcer disease, the prevalence ranging between 13 and 22% (Kudrow, 1980). Kudrow reported the prevalence to be 21.1% in a group of 119 male cluster headache sufferers compared to 10.7% in a group of age-sex matched migraineurs. A subsequent survey of 355 male cluster headache sufferers showed similar results. The prevalence in a group of 21 female sufferers was reported to be significantly different from the migraine 'controls', but twice the estimated incidence (2.5%) in the general population. The type of ulcer was noted to be predominantly duodenal (Kudrow, 1976c; Kudrow, 1980). Manzoni also reported a higher prevalence of 14.4% in his series (n=180) compared to 7.2 and 2.8% in the migraine and tension-type headache controls groups (each n=180). Peptic ulcer disease was more common in chronic than episodic cluster headache but

the patient numbers were markedly disproportionate with only 19 chronic sufferers (Manzoni *et al.*, 1983b). It has been unclear from the aforementioned reports whether the history of peptic ulceration relates to all-time prevalence, or in relation to the patients' cluster headache. With regard to the latter concomitant drug consumption was also not formally addressed. High gastric acid secretion after histamine stimulation was observed by Graham in 50% of patients (n=16), in some cases in the Zollinger-Ellison range (Sjaastad, 1992). However no study has addressed formally acid secretion during the acute attack, in the bout and out of the bout compared to a control group. If gastric acid secretion is truly elevated in cluster headache sufferers this may be a systemic manifestation of the associated parasympathetic discharge.

1.8.2 Cardiac disease

Coronary artery disease has also been reported to have a higher prevalence in cluster headache and has been associated with an abnormal lipid profile (Graham, 1972). Olesen has described type 2A and type 4 hyperlipidaemia in 2 brothers with cluster headache. Of 5 episodic and 6 chronic cluster headache sufferers 2 of the chronic cluster headache group had type 4 hyperlipidaemia, whilst the values in the episodic group were normal (Olesen, 1977). Although a casual link has been postulated, associated genetic loci may be more plausible. Kudrow reported the incidence of coronary heart disease in 119 cluster headache males to be 7.6% (mean age 43 years) compared to 3.6% of 140 non-cluster male controls (mean age 41 years), and 3% in the United States male population. The difference was not statistically significant. In contrast, improvement of angina during active bouts (Ekbom, 1970a) has been described. Bradycardia and hypertension (systolic and diastolic) have been consistently reported during spontaneous and provoked attacks of cluster headache, with an increase in heart rate just before the onset of the attack (Bruyn *et al.*, 1976; Ekbom, 1968;

Ekbom, 1970b; Jacobsen, 1969; Russell & Storstein, 1983; Russell & von der Lippe, 1982). Moreover, Jacobson found that neither symptoms nor the observed cardiovascular phenomena were altered by administration of intravenous atropine diphenhydramine or saline (Jacobsen, 1969); occlusion of the ipsilateral carotid artery resulted in marked sinus bradycardia and arrhythmia, supraventricular ectopics and sinus arrest without affecting the pain. Russell and Storstein formally assessed and heart rate with 24 hour Holter ECG monitoring and recorded paroxysmal atrial fibrillation, atrioventricular block and sinoatrial block in three patients during the acute attack (Russell & Storstein, 1983). Cardiovascular reflexes in cluster headache have been shown to be significantly different to controls. It has been suggested that the observed changes may be a response to pain. Some studies have suggested that heart rate and blood pressure changes are correlated with the degree of pain (Ekbom, 1970b) but other studies have not (Russell & Storstein, 1983). A more plausible and the most theorised concept is of central autonomic dysfunction. Cardiovascular disturbances in association with conditions affecting the central nervous system are well known (Vaisrub, 1975) and a central autonomic dysfunction is in keeping with the syndrome of cluster headache (Jacobsen, 1969; Russell & Storstein, 1983).

CHAPTER 2

Clinical Characteristics

2.1 Localisation of pain

The site of pain in cluster headache most commonly involves the ocular (retro-orbital and supra-orbital) and temporal regions, although the pain can be experienced over a wide area which includes the cheek, jaw, upper and lower teeth, nose, ear, occiput, neck, shoulder or whole hemicranium (Friedman & Mikropoulos, 1958; Kudrow, 1980; Manzoni *et al.*, 1983b; Sutherland & Eadie, 1972). The pain is usually strictly unilateral. More patients experience right than left sided attacks and 9-16% have experienced attacks on both the right and left side during different attacks. This is more common in different bouts, but can occur during the same bout (Friedman & Mikropoulos, 1958; Kudrow, 1980; Lance & Anthony, 1971; Manzoni *et al.*, 1983b; Sutherland & Eadie, 1972). Pain occurring simultaneously on both sides during an attack has been reported but is rare (Kudrow, 1980; Sjaastad *et al.*, 1985; Young & Rozen, 1999). A change of side within the same attack is even more rare (Sutherland & Eadie, 1972). The nature of the pain at worst is excruciating (Symonds, 1956) and has been described as ‘often one of the most severe forms of human suffering’ (Sutherland & Eadie, 1972). Very characteristically during the pain patients prefer to be active (Ekblom, 1970a; Kudrow, 1980; Manzoni *et al.*, 1983b; Russell, 1981).

2.2 Associated features

The pain of cluster headache is accompanied by ipsilateral autonomic symptoms suggesting a parasympathetic discharge and a sympathetic deficit. Most commonly observed are lacrimation, conjunctival injection, nasal congestion and rhinorrhoea (Table 2.1). Facial swelling and a partial Horner’s syndrome are less commonly noted

(Table 2.2). Facial swelling is usually localised orbitally/perio-orbitally. 'Lumps in the mouth' (Lance & Anthony, 1971) and focal palatal swelling (Kudrow, 1980) have been reported and may be a manifestation of mucosal oedema. The partial Horner's syndrome occurs during acute attacks but may persist between attacks (Drummond, 1988; Nieman & Hurwitz, 1961; Sutherland & Eadie, 1972). Patients have also described visual blurring on the side ipsilateral to the pain which may be due to the concomitant autonomic abnormalities. Some patients may experience generalised sweating during the attacks (Friedman & Mikropoulos, 1958; Lance & Anthony, 1971; Manzoni *et al.*, 1983b). Although earlier reports have suggested that nausea and vomiting do not occur (Horton, 1941), such symptoms have since been consistently reported with varying frequency, as has photophobia (Table 2.2).

There are also reports of other accompanying features during the attack such as anorexia and diarrhoea, facial hyperalgesia (Lance & Anthony, 1971), contralateral involuntary twitching of the foot (Sutherland & Eadie, 1972) and focal neurological symptoms. The described focal neurological symptoms have included visual disturbances such as flashing lights (Lance & Anthony, 1971), and scintillating scotomatous defect, contralateral facial and limb paraesthesia (Sutherland & Eadie, 1972) and vertigo and mild ataxia (Lance & Anthony, 1971). Aura symptoms in patients with cluster headache has been reported in 6 of 101 patients (4M, 2F) (Silberstein *et al.*, 2000). Five of the patients described visual and one described olfactory symptoms of 5-120 minutes duration associated with the cluster headache attack. One female patient had a history of migraine without aura, and two patients were noted to be related.

Associated Features in cluster headache

Table 2.1

Author	No. of patients in series	Lacrimation %	Conjunctival injection %	Nasal congestion (NC) and rhinorrhoea (R) %
(Friedman & Mikropoulos, 1958)	50	80	50	NC + R = 88
(Sutherland & Eadie, 1972)	58	62	45	NC = 35; R = 7
(Lance & Anthony, 1971)	60	82	45	NC = 47; R = 15
(Ekbom, 1970a)	105	82	84	NC + R = 68
(Kudrow, 1980)	500	84	78	NC + R = 72
(Manzoni <i>et al.</i> , 1983b)	180	84	45	NC = 48; R = 43

Table 2.2

Author	No. of patients in series	Facial swelling %	Partial Horner's syndrome %	Nausea %	Vomiting %	Photo-phobia %
(Friedman & Mikropoulos, 1958)	50	2	-	28 (+V)	-	22
(Sutherland & Eadie, 1972)	58	-	7	21(+V)	-	5
(Lance & Anthony, 1971)	60	10	32	43	15	20
(Ekbom, 1970a)	105	10	18	19	5	69
(Kudrow, 1980)	500	-	-	54	-	72
(Manzoni <i>et al.</i> , 1983b)	180	-	-	40	-	-

2.3 Duration and frequency of attacks

The reported duration of a single attack of cluster headache has varied from a few minutes up to a couple of days (Friedman & Mikropoulos, 1958; Sutherland & Eadie, 1972). Most attacks however last between 30 and 120 minutes (Table 2.3) and uncommonly last more than 3 hours (Sutherland & Eadie, 1972). The attacks occurring during the daytime prospectively recorded in one study, were found to be shorter than those at night, but this was not statistically significant (Russell, 1981). In Kudrow's series of 428 males and 72 females, the attack duration was longer in women (mean duration 90 minutes) than men (mean duration 60 minutes). The attack frequency can vary from one attack/week (Sutherland & Eadie, 1972) up to 8/day (Gardner *et al.*, 1947; Symonds, 1956). Patients most commonly experience 1-2 attacks/day; the median attack frequency is 1 attack/day (Ekbom, 1970a; Lance & Anthony, 1971; Manzoni *et al.*, 1983b ; Sutherland & Eadie, 1972). A higher frequency of attacks was observed in chronic compared to episodic cluster headache (Manzoni *et al.*, 1983b). Notably with regard to the shorter attacks and higher frequencies an overlap with paroxysmal hemicrania, first described in 1974 (Sjaastad & Dale, 1974), needs to be borne in mind.

2.3.1 Periodicity of attacks

The periodicity of attacks is a characteristic feature of cluster headache. Individual attacks tend to occur at the same hour. This pattern is however fragile and maintained usually for several days or weeks at a time. Thereafter the pattern of regularity may change or be lost altogether. This periodicity was observed by a number of authors (Ekbom, 1970a ; Horton, 1941; Sjaastad, 1992 ; Sutherland & Eadie, 1972 ; Symonds, 1956). Sharp peaks of onset of attacks was found by Manzoni *et al.* between 1-2am, 1-3pm and 9pm (Manzoni *et al.*, 1983b). A nocturnal preponderance for the attacks has been consistently observed (Friedman & Mikropoulos, 1958; Kudrow, 1980; Lance &

Anthony, 1971 ; Sutherland & Eadie, 1972 ; Symonds, 1956). Ekbom found a 62% incidence of nocturnal attacks, 8.6% exclusively nocturnal and 53.3% predominantly nocturnal (Ekbom, 1970c). Prospective collection of data from a total of 77 attacks in 22 patients showed that 75% of attacks occurred between 9 pm and 10 am, the highest frequency between 9 and 11 pm and from 4 to 10 am. Fifty-one percent of the attacks awoke the patient from sleep, including naps (assumed day-time) (Russell, 1981).

2.4 Episodic Cluster Headache - Duration and frequency of bouts of cluster headache

Most patients experience bouts lasting between 1-3 months during which cluster headache paroxysms can occur daily (Table 2.4) (Ekbom, 1947). However patients can experience ‘minibouts’ of daily paroxysms lasting a few days at a time (Sjaastad *et al.*, 1988) and some may experience isolated paroxysms during an otherwise entirely attack-free period (remission period) (Hornabrook, 1964). Eighty to 90% of sufferers have bouts which last less than a year (Table 2.4). Under current IHS classification criteria this group is defined as having episodic cluster headache. The definition of a remission period at the lower end of the scale is arbitrary but important for the sub-classification of cluster headache into episodic and chronic. Sutherland and Eadie have mentioned 10 days (Sutherland & Eadie, 1972), while the shortest period mentioned by Kudrow is 1 month (Kudrow, 1980). Current IHS guidelines have defined a remission period as at least 14 days (Headache Classification Committee of the International Headache Society, 1988). Conversely the longest remission periods reported have been 10 years (Symonds, 1956), 14 years (Sutherland & Eadie, 1972), 17 years (Ekbom, 1970a), 25 years (Hornabrook, 1964), and over 30 years (Graham, personal communication to Sjaastad (Sjaastad, 1992)). Kudrow has described two patients who had only 2 bouts at 20 year intervals (Kudrow, 1980). Most patients experience one bout a year (Table 2.4).

2.4.1 Periodicity of bouts

A seasonal preponderance of cluster headache bouts has suggested with onset of the bouts reported to occur mainly in the spring and autumn (Friedman & Mikropoulos, 1958; Hornabrook, 1964; Symonds, 1956). However, as with the predictability of cluster headache attacks within the bouts, Sutherland and Eadie encountered patients in whom the bouts seemed to have a regular seasonal incidence initially but where the patients were followed-up over a period of several years, the season of occurrence had often changed. Retrospective collection of reliable data from this series showed that although fewer bouts begin in the Australian autumn and early winter, there was no significant seasonal predilection for the onset of the bouts (Sutherland & Eadie, 1972). Manzoni commented from his series of 180 patients that no specific month seemed to predominate for the onset of the bouts; however, the most involved months seem to be February (24 patients) and March (20 patients). In those with season-bound bouts, these would recur mostly in the spring or autumn, or both, in 40% of the cases, and in summer or winter, or both, in 24% (Manzoni *et al.*, 1983b). Lance and Anthony did not find that the periodicity of the bouts occurred consistently upon the time of year (Lance & Anthony, 1971). Ekbom found that in 56% of cases the bouts mainly started in the autumn or spring (Ekbom, 1970a). A retrospective examination by Kudrow of the onset of 892 bouts from 404 male episodic cluster headache patients over a period of 1-10 years, showed that the frequency of the onset of the bouts increased with gradual increase or decrease of daylight throughout the year. Two significant peaks occurred 7-10 days after the longest and shortest days of the year (July and January). The gradual rise was interrupted twice showing a significant drop in frequency of bout onsets 7-10 days after the clocks were reset for Daylight Saving and Standard times in April and October (Kudrow, 1987).

2.5 Chronic Cluster Headache

Chronic cluster headache occurs in 10-20% of individuals with cluster headache. The current definition of chronic cluster headache is of 'attacks occurring for more than one year without remission or with remissions lasting less than 14 days'. This group of patients are further subdivided into primary chronic cluster headache, whereby the symptoms are unremitting from the onset of the condition, and secondary chronic cluster headache, where a chronic pattern of symptoms has developed following a period of episodicity (Headache Classification Committee of the International Headache Society, 1988). The original criterion for chronicity was proposed by Ekbom and de Fine Olivarius in 1971 (Ekbom & de Fine Olivarius, 1971). The relative frequency of primary and secondary chronic cluster headache is relatively consistent in different series. A slightly greater number of cases are seen in the primary chronic cluster headache group (ratios of primary to secondary 1.1:1 (Ekbom & de Fine Olivarius, 1971), 1.1:1 (Manzoni, 1998), and 1.5:1 (Kudrow, 1980)).

2.6 Differences Between Episodic and Chronic Cluster Headache

There are fundamentally few clinical differences between episodic and chronic cluster headache. The age of onset in the chronic cluster headache group is later (Kudrow, 1980; Manzoni, 1999). Consistently observed is the greater resistance to treatment in the chronic group compared to the episodic group; this has been observed for both preventative and abortive therapy (Gabai & Spierings, 1989; Gobel *et al.*, 1998; Kudrow, 1981). However this has not been formally shown because the small numbers in the chronic group have not allowed statistical inferences to be made. In addition individuals with the chronic form are far more susceptible to the attack triggering ability of substances such as alcohol and nitroglycerine. Manzoni observed the chronic cluster headache group to have a greater incidence of peptic ulceration (Manzoni *et al.*,

1983b) and head injury with and without loss of consciousness (Manzoni, 1999). With regard to the former the patient numbers were markedly disproportionate with only 19 chronic sufferers from a total of 180, and, most other studies addressing this issue (see Chapter 1) did not differentiate between the chronic and episodic form of the disorder. Kudrow studied 5 episodic and 5 chronic (1 female) cluster headache sufferers with nocturnal polysomnography (Kudrow *et al.*, 1984). All 5 of the episodic group were found to have sleep apnoea, 3 with central and 2 with obstructive sleep apnoea. One in the chronic group was found to have central sleep apnoea. In the sleep apnoea group the nocturnal attacks were more likely to be associated with REM sleep and preceding oxygen desaturation than the non-sleep apnoea group (all of whom had chronic cluster headache). This was consistent with a similar observation in another small chronic group (n=4) of no evidence of sleep apnoea and no differences in sleep pattern during a symptom-free and symptomatic night; but there was a decrease in total time of REM sleep and increase in stage 3 and 4 sleep (Dexter, 1984). It was commented upon by Kudrow *at al.* that sleep apnoea is observed in up to 62% of males in the population aged over 55 years; all but one (age 37 years) of the episodic group was aged over 55 years. In addition the number of patients and the number of attacks studied were small. HLA typing has been done in 42 patients with cluster headache, 37 with the episodic and 5 with the chronic form. The histocompatibility antigen A1 was found in all the chronic sufferers but not in the episodic group (Cuppers & Altenkirch, 1979) as demonstrated in an earlier study (Kudrow, 1978); whether the patients had primary or secondary cluster headache was not mentioned. Support for a genetic predisposition to cluster headache has been discussed in Chapter 1; HLA antigen subtyping may provide insights into those individuals who have a genetic susceptibility to the development of chronic cluster headache.

2.7 Symptomatic Cluster Headache

Cluster headache associated with intracranial pathology has been reported for different lesions at different anatomical sites. These include pituitary tumours (Greve & Mai, 1988; Hannerz, 1989; Porta-Etessam *et al.*, 2001; Tfelt-Hansen *et al.*, 1982) meningioma of the cervical canal (Kuritzky, 1984), aneurysm of the anterior communicating artery (Greve & Mai, 1988), posterior communicating artery (McBeath & Nanda, 2000) arteriovenous malformations (Mani & Deeter, 1982; Munoz *et al.*, 1996), vertebral artery aneurysm (West & Todman, 1991) and nasopharyngeal carcinoma at the skull base (Mathew, 1992). In some of the reports patients have been described to have a typical and longstanding history of cluster headache. An intracranial lesion has been subsequently found on investigation and attacks have ceased following treatment of the lesion (Hannerz, 1989; Mani & Deeter, 1982; West & Todman, 1991). The histories in these latter cases are consistent with a coincidental relationship between cluster headache and the intracranial pathology. Moreover the cessation of the attacks due to surgical intervention *per se* must be considered. There are reports however of intracranial lesions occurring in close temporal relation to the onset of cluster headache attacks or worsening of existing symptoms, with resolution of the attacks with treatment of the lesion (Greve & Mai, 1988; Kuritzky, 1984; McBeath & Nanda, 2000; Munoz *et al.*, 1996; Porta-Etessam *et al.*, 2001; Tfelt-Hansen *et al.*, 1982). Of particular note is that some of these cases did not respond to appropriate medical treatments for cluster headache (Greve & Mai, 1988; Kuritzky, 1984; McBeath & Nanda, 2000) whilst others did respond to such treatments (Tfelt-Hansen *et al.*, 1982). In addition the symptoms are usually typical and consistent with IHS classification criteria (Greve & Mai, 1988; Kuritzky, 1984; Tfelt-Hansen *et al.*, 1982). However there may some more atypical features such as longer attack duration (Munoz *et al.*, 1996), although again this has been reported for non-symptomatic cases (Sutherland & Eadie, 1972).

2.8 Post-traumatic cluster headache

There have been a number of reports of cluster headache associated with trauma. Lance and Anthony reported 8 patients of their 60-patient series (13%) to have experienced a head injury (Lance & Anthony, 1971). Although in 4 patients the site of the original injury was the same as the side of the cluster headaches, the temporal relationship was not close (21 months, 7, 8 and 30 years). The range in the 8 patients was 2 months to 30 years. Friedman commented upon a past history of 'some type of head injury with or without loss of consciousness in 16%' of his series (Friedman & Mikropoulos, 1958). Symonds reported head injury in 2 of his 17 (12%) cases; again although the site of the injury in both cases coincided with the side of the cluster headache attacks, the onset occurred 5 and 25 years later (Symonds, 1956). Manzoni found that 36.9% of patients in his series of 374 male sufferers, gave a past history of head injury, 13.4% with loss of consciousness (Manzoni, 1999). However head injury followed the onset of cluster headache in 22% of the cases. In the rest of the cases the average time elapsed between the head injury and cluster headache onset was 10 years. The frequency of head injury was higher in the chronic group, particularly secondary chronic cluster headache. Kudrow did not find a correlation with head injury in his large series; he reported a history of significant head injury in 5.2% of patients (Kudrow, 1980). Reik described 3 cases of cluster headache onset in close temporal relation to head injury (from immediately to 1 month after the injury); 2 patients gave a history of primary chronic cluster headache and one patient gave a history of bouts of variable duration (from 1 to 18 months) interspersed by remission periods (Reik, 1987). Turkewitz reported on the almost immediate onset of cluster headache following minor head injury without loss of consciousness; the symptoms were consistent with primary chronic cluster headache with cessation of attacks after 2 years, the time at which the report was written (Turkewitz *et al.*, 1992). Mathew and Rueveni presented a series of patients with onset

of cluster headache attacks with significant temporal relation to head injury or a surgical procedure (Mathew & Rueveni, 1988). The side of the attacks corresponded to the side of maximal trauma, the symptoms were of the primary chronic type and response to treatment was less satisfactory compared to the idiopathic syndrome.

The syndrome of post-traumatic headache can be likened to that of true symptomatic cluster headache. The precipitated cluster headache attacks seem to adopt a primary chronic pattern. The relevance of head past head injury to the development of cluster headache remains uncertain. It has been postulated that this may relate to behavioural and lifestyle patterns (Manzoni, 1999).

Attack duration and frequency

Table 2.3

Author	No. of patients in series	Duration of attacks (minutes)	Attack frequency
(Friedman & Mikropoulos, 1958)	50	30-120 in 86% range – ‘some minutes up to 360’	2/week to 4/day 1-3/day in 90%
(Sutherland & Eadie, 1972)	58	<30- 11% 30 to 120-50% 120 to 180-17% 180 to 360-13% over 360 – 9%	<1/day-28% 1/day-40% 2-3/day-30% 4-6/day-2%
(Lance & Anthony, 1971)	60	Shortest 10 longest 480 usually 10-120	1-3/day up to 8/day
(Ekblom, 1970a)	105	<30-180 30-120 in 63%	<1 to >3/day 1-2/day in 78%
(Manzoni <i>et al.</i> , 1983b)	180	30-120 in 73%	Usually 1-2; range <1-5
(Kudrow, 1980)	500	30-120	2/week to 8+/day

Bout duration and frequency

Table 2.4

Author	No. of patients in series	Duration of bouts (weeks)	Remission periods (months)	No. bouts/year
(Friedman & Mikropoulos, 1958)	33?	1-16 6-8 in 50%	3-60 usually 7-18	1/yr in 54% 1/1.5-2yrs in 44%
(Ekbohm, 1970a)	88	1-12+; 4-12 in 72%	-	<1/yr-14% 1/yr -40% 2/yr 31% >2/yr-16%
(Lance & Anthony, 1971)	48	2-12 in 73%	-	-
(Sutherland & Eadie, 1972)	48	0-4 in 23% 5-13 in 45% 14-26 in 19% 27-52 in 4%	<3 in 15% 3-6 in 15% 6-12 in 12% 1-5 in 44% >5 in 15%	-
(Kudrow, 1980)	428	median <8	median 7-12 <1yr in 67% <2yrs in 81%	-
(Manzoni <i>et al.</i> , 1983b)	161	4-8 in 78%	-	1-2/yr in 73%

CHAPTER 3

The Pathophysiology of Cluster Headache

3.1 The pain phenomenon

Work done in the early part of the twentieth century (Feindel *et al.*, 1960; Penfield & McNaughton, 1940; Wolff, 1963) identified the principal intracranial pain-producing structures to be the blood vessels, particularly the proximal cerebral and dural arteries, and the large veins and venous sinuses. Stimulation (Wolff, 1963) or distension (Martins *et al.*, 1993; Nichols *et al.*, 1990) of different vessels will refer pain to different parts of the head. These studies formed part of the basis for the concept of a *vascular* origin to the primary headache syndromes of migraine and cluster headache. The throbbing quality of pain and relief from the vasoconstrictive agent, ergotamine, has lent further weight to this view (Duvoisin *et al.*, 1961; Graham & Wolff, 1938). However migraine and cluster headache are clinically, epidemiologically and in terms of management very distinct (Lance & Goadsby, 1998). Moreover clinical studies (Drummond & Lance, 1983; Drummond & Lance, 1984) have suggested a dissociation between the vascular phenomena and clinical manifestations.

Surrounding the large cerebral vessels, meningeal vessels, large venous sinuses and dura mater is a plexus of largely unmyelinated fibres which arise mainly from the ophthalmic division of the trigeminal nerve with some contribution from the maxillary division of the trigeminal nerve, and in the posterior fossa from the upper cervical dorsal roots. Branches of the vagal and glossopharyngeal nerves contribute to the innervation of the posterior circulation and dura mater of the posterior fossa (Moskowitz, 1990; Penfield & McNaughton, 1940). The trigeminal fibres arise from neurons in the trigeminal ganglion. The central axon of the cell body in the trigeminal

ganglion descends in the spinal tract of the trigeminal nerve to the second segment of the spinal cord. Here fibres from the posterior part of the head traverse the dorsal root ganglion to converge on second order neurons in the dorsal horn and subsequently ascend in the contralateral spinothalamic tract to connections in the brainstem (nucleus gigantocellularis, midbrain reticular formation, periaqueductal gray) and diencephalon (hypothalamus), and thence ultimately to the thalamic nuclei and the cerebral cortex. Functionally the trigeminal nucleus extends beyond the traditional nucleus caudalis to the dorsal horn of the high cervical region. In the cat, stimulation of either the superior sagittal sinus or the greater occipital nerve results in increased metabolism in both the trigeminal nucleus and the dorsal horn at C1 and C2 (Goadsby *et al.*, 1997; Kaube *et al.*, 1993). Exteroceptive sensation from the concha of the ear is carried by the vagus nerve to the jugular ganglion and also terminates within the spinal nucleus of the trigeminal nerve. Transmission of pain is controlled by the endogenous pain control system descending from the region of the periaqueductal gray, raphe nuclei and locus coeruleus, to the spinal interneurons in the spinal trigeminal nucleus and dorsal horn of the upper cervical cord (Basbaum & Fields, 1978).

It is clear that the trigeminal nerve is implicated in the pain of cluster headache - the pain is unilateral and located predominantly within the distribution of the first division of the trigeminal nerve. Pain can radiate to regions in the distribution of the maxillary division, upper cervical roots and vagal nerve (see Chapter 2). Lesions aimed at the trigeminal nerve and ganglion are the most effective surgical therapeutic procedures (see Chapter 4). There is asymmetry of blink reflexes during the active bout (Pavesi *et al.*, 1987); and, in vivo activation of the trigeminal and parasympathetic systems during acute attacks of cluster headache has been shown (Goadsby & Edvinsson, 1994a). The latter showed an increase in internal jugular CGRP, a marker for trigeminal activity, and

VIP, a marker for parasympathetic activity (Edvinsson, 2001) during the acute cluster headache attack. Both levels returned to normal after treatment of the attack.

3.2 The autonomic phenomena

The autonomic features of cluster headache are characterised by a parasympathetic discharge and sympathetic deficit on the side ipsilateral to the pain during the acute attacks.

Parasympathetic fibres originate in the superior salivatory nucleus. The fibres traverse the facial nerve and the greater superficial petrosal nerve to join the vidian nerve (the greater superficial petrosal nerve and greater deep petrosal nerve join to form the vidian nerve) and synapse in the pterygopalatine ganglion. Post ganglionic fibres loop back as orbital rami to the cavernous sinus and internal carotid artery where they form a plexus with sympathetic and trigeminal fibres (ophthalmic and maxillary division fibres), before advancing to supply the lacrimal glands and circulation of the forehead. Sympathetic fibres arise from the superior cervical ganglion and course along the internal carotid artery, through the cavernous sinus to the long ciliary nerve which innervates the dilator pupillae. Some fibres follow the external carotid artery and innervate Müller's muscle of the eyelid, and the blood vessels and sweat glands of the face except for sweating of the medial aspect of the forehead, which follows the internal carotid artery (Drummond & Lance, 1992).

The parasympathetic discharge in cluster headache is manifested by lacrimation, conjunctival injection, nasal secretion, nasal congestion and facial swelling (see Chapter 2). Saunte has quantified lacrimation during the acute attack and found this to be increased on the side ipsilateral to the pain by a factor of about two. Lacrimation also occurred on the non-symptomatic side but by a factor of 1.4. Similarly nasal secretion

was increased bilaterally during the acute attack, but this was greater on the symptomatic side compared to the asymptomatic side (Saunte, 1984). The conjunctival injection, nasal congestion and facial swelling are suggestive of extracranial vasodilatation. This is supported by an increase in corneal temperature, corneal indentation pulse amplitudes and intraocular pressure during the acute attack. The changes seen in corneal indentation pulse amplitudes and intraocular pressure were bilateral but most pronounced on the symptomatic side, while corneal temperature increases occurred only on the side ipsilateral to the pain during the attack. No such changes have been observed in migraineurs during and between attacks of pain (Sjaastad, 1992; Sjaastad *et al.*, 1985). In addition, during spontaneous and induced attacks of cluster headache thermographic measurements have shown an increase in temperature of the affected orbital and maxillary region (Drummond & Lance, 1984). Salivation is diminished during the attack; it has been suggested that sympathetic activity dominates over parasympathetic action on the salivary glands but is unable to override its lacrimal and vascular functions (Saunte, 1984). This may be part of a generalised sympathetic arousal distinct from the observed local sympathetic deficit. It is most likely that the parasympathetic discharge is mediated via the greater superficial petrosal nerve (Drummond, 1988). Increase in cutaneous blood flow has been observed to follow the onset of pain and has been therefore considered to be a secondary phenomenon; a vasodilator reflex mediated by the trigeminal nerve as the afferent arm and the greater superficial petrosal nerve as the efferent arm (Goadsby & Lance, 1988).

The sympathetic deficit manifests as a partial Horner's syndrome ipsilateral to the pain. These symptoms occur during the attacks but have also been found to persist in between attacks (Nieman & Hurwitz, 1961; Sutherland & Eadie, 1972). Nieman and Hurwitz found a permanent deficit in 10 of 50 cases (Nieman & Hurwitz, 1961), while a subtle

permanent sympathetic deficit on the asymptomatic side has also been reported (Fanciullacci *et al.*, 1982; Micieli *et al.*, 1988). In attempt to determine the site of the sympathetic deficit - 1st (central), 2nd (preganglionic) or 3rd (postganglionic) order neuron Fanciullacci *et al.* studied pupil responses to thymoxamine (selective α_2 blocker), 4% cocaine (a re-uptake inhibitor), 2% tyramine (releases noradrenaline from the nerve terminals) and 1% phenylephrine (direct sympathomimetic agent), in individuals with cluster headache whilst asymptomatic, during and out of the active bout (Fanciullacci *et al.*, 1982). Cocaine dilatation has been shown to be reduced in any Horner's syndrome regardless of site. Tyramine will dilate the pupil normally in cases with a central or preganglionic lesion, but the reaction is reduced in a postganglionic lesion. When sympathetic innervation is impaired, sympathetically innervated effector cells become supersensitive to directly acting sympathomimetic agents at weak concentrations ordinarily ineffective; a denervated muscle (postganglionic lesion) is more sensitive to such drugs than a decentralised lesions (central and preganglionic) (Thompson & Mencher, 1971). Baseline pupil diameters were not statistically significant. There was no asymmetry in response to thymoxamine. There was bilateral mydriasis in response to topical cocaine and tyramine, but this was significantly reduced on the symptomatic side compared to the asymptomatic side. Although this study found an insignificant anisocoria with smaller dilatation on the symptomatic side with phenylephrine, other studies have shown excessive dilatation of the pupil suggestive of denervation supersensitivity of the receptors (Salveson & Sjaastad, 1987; Thompson & Mencher, 1971). Deficient pupillary dilatation to hydroxy-amphetamine (which also releases noradrenaline from the nerve terminals) on the symptomatic side has been shown to be accompanied by a similar deficiency of sweating of the medial aspect of the forehead, with overactivity of the sweat glands in this region in response to circulating pilocarpine (Salveson & Sjaastad, 1987). The studies therefore suggest the



lesion to be postganglionic. But it has been acknowledged that the pupil responses to the different agents studied is not as clear cut as defined above (Fanciullacci *et al.*, 1988; Salveson *et al.*, 1987; Thompson & Mencher, 1971). The matter is not further clarified by the response to intravenous clonidine, an inhibitor of central sympathetic activity; this resulted in more marked miosis bilaterally (compared to the control group) in cluster headache sufferers (ECH during active bout but outside an attack) but more marked on the symptomatic side. Tyramine alone caused bilateral mydriasis significantly less on the symptomatic side. Clonidine administration before tyramine resulted in an increase in mydriasis compared to tyramine alone on the asymptomatic side (Fanciullacci *et al.*, 1988). In another study Fanciullacci and colleagues showed that lithium induced a symmetrical response to tyramine, postulating this to be a correction of abnormal asymmetries in central neuronal systems which regulate autonomic function (Fanciullacci *et al.*, 1983).

3.3 Pathophysiological hypotheses

There have been two main theories regarding the pathophysiology of cluster headache. These have addressed pathology in the region of the superior pericarotid cavernous sinus plexus and the hypothalamus. Dysfunction of the carotid body chemoreceptors has also been postulated.

3.3.1 A pathophysiological focus in the region of the pericarotid cavernous sinus

It has been postulated that the predominantly first division trigeminal pain, parasympathetic discharge and sympathetic deficit during cluster headache attacks could be explained by a lesion in the region of the cavernous sinus. It has been suggested that the syndrome may be explained by a pathophysiological focus located in the superior pericarotid cavernous sinus plexus in which fibres from the ophthalmic

division of the trigeminal nerve, the maxillary division, the superior cervical ganglion, and the pterygopalatine ganglion, all join together (Hardebo, 1990; Moskowitz, 1988). Orbital phlebographic findings during cluster headache attacks have been found to be abnormal on the symptomatic side only, and bilaterally but with greater changes on the symptomatic side. The most frequent findings were of narrowing of the entire superior ophthalmic vein or of the third segment of the vein; two of the 8 patients with abnormal imaging (from a total of 13) had partial occlusion of the cavernous sinus and collateral veins in the region of the superior orbital fissure (Hannerz *et al.*, 1987). The changes observed were similar to those seen in patients with Tolosa-Hunt syndrome (Hannerz *et al.*, 1986). Magnetic resonance angiography in a single case report of a spontaneous attack of cluster headache has shown dilatation of the ipsilateral ophthalmic artery, with normal repeat angiographic findings during remission (Waldenlind *et al.*, 1993). Dilatation of the ipsilateral ophthalmic artery with localised narrowing of the extradural part of the internal carotid artery has been shown on carotid angiography during a cluster headache attack occurring 15 minutes after left internal carotid artery puncture (Ekbom & Greitz, 1970). Cluster headache has therefore been attributed to an inflammatory process occurring in the cavernous sinus and tributary veins. It has been proposed that inflammation obliterates the venous outflow from the cavernous sinus on one side, thus injuring traversing sympathetic fibres of the intracranial internal carotid artery and its branches. It is further theorised that the active period ends when the inflammation is suppressed and the sympathetic fibres fully or partially recover (Hardebo, 1994). This hypothesis was supported by Gawel *et al.* who used gallium single photon emission computerised tomography (SPECT) to study patients with cluster headache, on the basis that the tracer is picked up in areas of inflammation such as sarcoid and allergic alveolitis. In 3 of 6 patients imaged with gallium SPECT during the active bout, increased activity was seen in the parasellar region and faded in one

patient as the patient came out of the active bout (Gawel *et al.*, 1990). More recently increased activity in the region of the cavernous sinus was reported in a positron emission tomography (PET) study of four patients imaged during nitroglycerine (GTN)-induced attacks of cluster headache (Hsieh *et al.*, 1996a). In a study of 23 patients who had examination of the cerebrospinal fluid (CSF) during an active bout but whilst headache-free, 15 of 37 samples from 12 patients showed a raised CSF protein. Three of 32 samples showed a pleocytosis greater than 5 mononuclear leucocytes, while only 2 controls of 256 showed a white cell count greater than 3 (Hardebo & Ryberg, 1989). The prompt response to high dose corticosteroids (Jammes, 1975) was thought to be consistent with an inflammatory process. Although structural imaging with computerised tomography (CT) has been normal in most patients with cluster headache (Russell *et al.*, 1978), symptomatic cases of cluster headache from lesions in the region of the cavernous sinus have been reported (Greve & Mai, 1988; Hannerz, 1989; Tfelt-Hansen *et al.*, 1982). Craniometric measurements in patients with cluster headache have been found to be abnormal compared to age matched controls and migraineurs prompting the authors to postulate that the cavernous sinus in the cluster headache patients may also be morphologically abnormal (Afra *et al.*, 1998). The bilaterality of the autonomic symptoms and of the pain (side shift, and less commonly bilaterality of the attack) has been explained by a lesion in this region since the cavernous sinus is bilateral and paired structure (Moskowitz, 1988). The precipitation by vasodilators such as GTN and histamine (see Chapter 1) and resolution with vasoconstrictors such as sumatriptan and ergotamine (see Chapter 4) has been thought in keeping with a primary vascular pathogenesis. Moskowitz has suggested that the circadian and circannual pattern of symptoms may be explained by involvement of that portion of the hypothalamic blood supply provided by arterial branches from the cavernous portion of the internal carotid artery which has been shown with carotid angiography to be

narrowed during the acute attack (Moskowitz, 1988).

However activation in the region of the cavernous sinus during gallium SPECT has been observed in chronic cluster headache, episodic cluster headache in and out of the bout and also in migraineurs (Sianard-Gainko *et al.*, 1994). Increased activity in this region imaged with PET has been observed during capsaicin-induced first division trigeminal pain (May *et al.*, 1998b). The abnormal findings on orbital phlebography are not specific to cluster headache and have been observed in migraine, tension-type headache and 'cervicogenic headache' (Bovim *et al.*, 1992). Symptomatic cluster headache has been reported not only for lesions in the region of the cavernous sinus but lesions at different anatomical sites such as the upper cervical canal (Kuritzky, 1984), the occipital lobe (Mani & Deeter, 1982), the vertebral artery (West & Todman, 1991) and the skull base (Mathew, 1992). Moreover an inflammatory hypothesis would have to account for longstanding recurrent episodes of inflammation with precise onset of bouts, spontaneous resolution and no residual morbidity or mortality. The periodicity of cluster headache is a key feature of the syndrome. The precise circadian and circannual pattern of symptoms are more suggestive of primary dysfunction of the central nervous system.

3.3.2 Central pathophysiological mechanisms involving the hypothalamus

The onset of cluster headache bouts has been suggested to have a seasonal preponderance, occurring maximally in autumn and spring. Most of the reported observations have been retrospective (see Chapter 2). The largest of these was reported by Kudrow who showed that two significant peaks of onset of cluster headache bouts occurred 7-10 days after the longest and shortest days of the year (July and January). The gradual rise was interrupted twice showing a significant drop in frequency of bout

onsets 7-10 days after the clocks were reset for Daylight Saving and Standard times in April and October (Kudrow, 1987). These results were interpreted to indicate that the frequency of cluster bout onsets increased as photoperiods lengthened or shortened. Artificial interruption of the photoperiods such as changing of the clocks, resulted in sharp decreases in the frequency of cluster bout onsets, ruling out temperature influences. It was speculated that the onset of cluster bouts was due to an inability to synchronise the internal circannual pacemaker, the hypothalamus, to environmental light cues. Patients with bipolar affective disorders demonstrate exacerbation of symptoms associated with changes in photoperiods and respond to resetting of the internal pacemaker with bright-light therapy (Lewy *et al.*, 1987).

Over 50% of cluster headache attacks occur at night, commonly occurring 1-2 hours after falling asleep or during the early hours of the morning (Ekbom, 1970a; Russell, 1981). In a prospective study of 22 patients, Russell documented that 39 of 77 spontaneous attacks awoke the patients from sleep (Russell, 1981). Dexter and Weitzman carried out polygraphic sleep recordings in three cluster headache patients with nocturnal attacks. Five of the nine arousals with headache occurred directly from REM sleep; three within 3 min after rapid eye movement (REM) sleep, and one between 3 and 9 min after a REM sleep period (Dexter & Weitzman, 1970). Kudrow showed that 52% of nocturnal attacks (total 19), studied in 10 patients, occurred in REM sleep (Kudrow *et al.*, 1984) and Manzoni confirmed such findings in overnight electroencephalogram (EEG) recordings in 2 patients (Manzoni *et al.*, 1981). Although this has not been supported by other authors (Pfaffenrath *et al.*, 1986; Sjaastad, 1992 ; Waldenlind & Gustafsson, 1987), it is in keeping with the observations of Bono *et al.* who showed that the benzodiazepine triazolam, which acts by delaying the REM cycles, reduced the occurrence of nocturnal attacks in 20 patients with episodic cluster

headache with predominantly nocturnal symptoms (Bono *et al.*, 1985). The same group showed that sleep deprivation had a short and long term effect in preventing attacks of cluster headache.

Disturbance of hypothalamic function during the active cluster bout is supported by a number of studies which have shown abnormalities of hypothalamic-determined functions:

Cortisol: Cortisol shows a diurnal pattern of secretion with trough nocturnal levels and high morning levels on waking. The mean 24 hour cortisol levels are higher during the active bout compared to out of the bout (Waldenlind *et al.*, 1987) and to non-headache controls (Facchinetti *et al.*, 1986). Facchinetti *et al.* attributed this to stress experienced during the active bout, but also showed a phase-advance in circadian pattern of secretion of about 2 hours. In a study of 11 patients during the active bout (10 males, 1 female) compared to 8 controls, the typical circadian pattern of secretion was noted to be blunted, and again there was a significant phase-advance in the circadian pattern of secretion (Chazot *et al.*, 1984).

Melatonin: Melatonin has a strong circadian rhythm and is produced in the pineal gland. It is converted from serotonin to melatonin. This is largely regulated by N-Acetyltransferase. Regulation of enzymatic activity responsible for the circadian oscillations of melatonin is by the suprachiasmatic nucleus of the hypothalamus which is innervated by retino-hypothalamic fibres. Melatonin is produced at night and its production ceases in response to retinal stimulation by sunlight via the retino-hypothalamic fibres. Melatonin secretion is therefore very sensitive to light-dark cycles and therefore photoperiodicity (Brezinski, 1997). Chazot *et al.* showed that in 11

patients during the active bout compared to 8 controls nocturnal melatonin levels were blunted with a slightly advanced phase of secretion; one patient showed complete abolition of the circadian pattern of secretion. The 3 patients who had the lowest melatonin plasma levels had the largest cortisol phase-shift (Chazot *et al.*, 1984). Waldenlind *et al.* confirmed lower nocturnal melatonin levels during the active bout compared to the inactive period (Waldenlind *et al.*, 1987). The main metabolite of melatonin is 6-sulphatoxymelatonin. Leone *et al.* have shown higher nocturnal than day-time urine levels of the metabolite in controls (n= 14), while no difference between night and day-time secretion was seen in 20 cluster headache sufferers during the active bout and 13 of this group re-tested in the remission period. Moreover nocturnal secretion in and out of the active bout was lower than nocturnal secretion in the control group (Leone *et al.*, 1998).

Prolactin: The normal pattern of secretion of prolactin is of a nocturnal peak and diurnal trough. Polleri studied the diurnal variation of prolactin in 9 individuals with active cluster headache (4 ECH, 5 CCH) compared to 7 with atypical facial pain and 10 healthy volunteers (Polleri *et al.*, 1982). The mean levels of prolactin did not differ between the three groups. However, the circadian rhythm of secretion was not present in individuals with cluster headache, but persisted in those individuals with atypical facial pain and in the control group. Although lithium reduced the frequency and severity of cluster headache attacks, it was ineffective in inducing periodicity of prolactin secretion (lithium levels sub-therapeutic at 0.4-0.6 mEq/l despite clinical response). Boiardi and colleagues found no difference in basal prolactin levels in patients with cluster headache compared to controls, and no difference in prolactin responses to insulin, levodopa or thyrotropin releasing hormone (TRH) between the two groups; whether the patients were in or out of the active bout was not clear (Boiardi *et*

al., 1983). Bussone and colleagues (Bussone *et al.*, 1988) have found basal prolactin levels to be similar in individuals with active cluster headache compared to controls, while others have also suggested a disruption of circadian rhythm of prolactin secretion in cluster headache (Ferrari *et al.*, 1983). Waldenlind and Gustafsson have reported lower mean 24-hour serum prolactin levels during the remission period and during the active bout compared to controls, but the difference was not statistically significant. An increase in secretion was also reported to coincide with acute attacks of pain (Waldenlind & Gustafsson, 1987, Polleri *et al.*, 1982). Chazot however did not find any change in diurnal prolactin secretion in his group of 11 individuals during the active bout compared to controls. In addition the increases in prolactin secretion did not coincide with acute attacks (Chazot *et al.*, 1984).

Growth hormone: The levels of growth hormone show a nocturnal surge in the first 2 hours of sleep, a profile which may disappear later in adult life. Chazot showed a bimodal growth hormone profile as a result of an advance in the growth hormone peak in the evening in some of his 11 patients during the active bout (Chazot *et al.*, 1984). Boiardi *et al.* reported normal basal growth hormone levels in 10 patient compared to 10 matched controls. A normal growth hormone response to insulin, L-Dopa and thyrotropin releasing hormone (TRH) was also seen suggesting intact hypothalamic-pituitary regulation (Boiardi *et al.*, 1983).

Thyroid stimulating hormone (TSH) and Thyrotropin releasing hormone (TRH) responses: Bussone found that although basal TSH levels were increased in 10 individuals with cluster headache during the active bout and 12 out of the bout compared to 7 controls, the difference was not significant (Bussone *et al.*, 1988). There was no difference in the TSH and prolactin response to TRH in the three groups.

Maximum prolactin increase after TRH administration was not significantly different between the groups but maximal TSH increase was significantly lower in cluster headache sufferers during the active bout compared to those in remission and compared to controls. Waldenlind and Gusafsson did not find significant differences between basal serum levels of T3, T4 and TSH in 31 cluster headache sufferers compared to 14 controls. When 16 cluster patients (11 male, 5 female) were used as their own controls, there was no significant difference in the prolactin or TSH response to TRH between the cluster period and remission. In women with ECH compared to controls there was a significantly lower response to TRH for prolactin during and out of the active bout and for TSH during active bouts (Waldenlind & Gustafsson, 1987).

Gonadal hormones: A number of studies have shown decreased levels of testosterone (total) in patients with cluster headache. Kudrow found decreased serum testosterone in two small studies groups (n=9 and 6) during the active bout compared to the remission period and the control group. The levels in the remission period were also lower than levels in the control group in one of the studies (Kudrow, 1976a). The lower levels during the active bout compared to remission were confirmed in 5 individuals investigated both during and out of the active bout (Kudrow, 1980). However these findings were not reproduced by Nelson who found no difference in testosterone levels between individuals with cluster headache studied in the headache-free phase during the active bout (n=31; 5 also investigated out of the active bout) and migraine (n=34; 8 investigated during a migraine attack) (Nelson, 1978). Similarly Romiti *et al.* did not find any significant difference in testosterone levels between individuals with cluster headache in remission (n=25) compared to 'controls' (n=29) who suffered other types of headache, which were not defined. In 11 patients with ECH there was a significant reduction in mean testosterone levels during the acute attack compared to the

interparoxysmal period (Romiti *et al.*, 1983). Facchinetti *et al.* also found lowered mean serum testosterone in individuals with cluster headache (n=9; ECH) and an approximately 2 hour phase delay in circadian pattern of secretion during the active bout compared to controls (n=7) (Facchinetti *et al.*, 1986). Murialdo *et al.* found this to be the case in the chronic variety only (20 ECH, 14 CCH, 39 controls) (Murialdo *et al.*, 1989), while Fanciullacci *et al.* found significantly higher levels in patients compared to controls (number of patients not known) (Fanciullacci *et al.*, 1987). Waldenlind and Gustafsson found the 24 hour mean testosterone levels to be comparable in cluster headache individuals in and out of the active bout, and in controls. The diurnal variation was blunted in 11 males in the active compared to the remission period. Serum oestradiol level taken thrice in 24 hours were not significantly different in cluster headache sufferers in and out of the active bout (33 M, 14 F) compared to controls (Waldenlind & Gustafsson, 1987). In 7 of 8 men investigated in and out of the bout the 0200 oestradiol level was lower in remission compared to the active period but the difference was not significant.

Gonadotrophins: Luteinising hormone (LH) also shows a nocturnal surge. Facchinetti *et al.* showed basal mean levels in individuals with active cluster headache (n=9) to be similar to controls (n=7) (Facchinetti *et al.*, 1986), although Kudrow found lower levels in the active bout compared to the remission period in 4 sufferers (Kudrow, 1980). Micieli *et al.* found LH pulsatility to be disordered during the active compared to the remission period (n=12) (Micieli *et al.*, 1987). Murialdo *et al.* found mean basal LH levels to be similar to controls but basal follicle stimulating hormone (FSH) levels to be higher than controls. The peak value of LH after intravenous luteinising hormone releasing hormone (LHRH) was decreased in CCH but not ECH in and out of the active bout. The FSH response to LHRH was significantly higher in all sub-groups of

individuals with cluster headache than in healthy subjects (Murialdo *et al.*, 1989). Basal and peak follicle stimulating hormone after intravenous LHRH was significantly elevated in both ECH and CCH. Fanciullaci *et al* found the peak LH response to LHRH was comparable to a control group in 27 men with cluster headache; there was no difference between the active and remission periods and in individuals with ECH and CCH. However the peak FSH response to LHRH was significantly greater in individuals with cluster headache compared to controls. The response appears to have been greater in CCH than ECH in the active bout (Fanciullacci *et al.*, 1987). Waldenlind and Gustafsson did not find a significant difference between individuals with cluster headache in and out of the bout, and controls, in the secretion pattern of FSH and LH, and the gonadotrophin response to TRH (Waldenlind & Gustafsson, 1987).

Conclusion

The data suggests dysfunction of the neuroendocrine system in individuals with cluster headache. There is preservation of the hypothalamic-pituitary axis and the abnormalities are more supportive of a primary dysfunction of the hypothalamus. The pain, although strictly unilateral, can change sides and rarely is bilateral. The autonomic features which accompany the pain are clinically unilateral but sub-clinically bilateral. The hypothalamus is a bilateral paired structure which could account for these phenomena. The studies detailed above suggest abnormalities not only during the active bout but also in the remission period. This would be in keeping with the observed persistence of autonomic deficit observed in some individuals in the remission period. But how does dysfunction of the hypothalamus lead to the head and facial pain syndrome of cluster headache?. Current theories have addressed central pain mechanisms involving an imbalance of the trigeminal nociceptive and midbrain endogenous antinociceptive system, autonomic control of cerebral and dural blood flow, and descending pathways

from the cortex and hypothalamus (Goadsby & Lance, 1988). Dysfunction of the hypothalamus may trigger a centrally driven autonomic disturbance, accompanied by a disruption of the balance between the trigeminal nociceptive and the antinociceptive systems. This concept is supported by the observed dichotomy between the autonomic features and pain as reported by Maxwell in a patient with CCH who underwent therapeutic percutaneous radiofrequency trigeminal ganglio-rhizolysis. The patient continued to experience attacks of 'a hemicranial flush, mild tearing and a sense of nasal stuffiness and fullness but no associated pain' (Maxwell, 1982).

3.3.3 The role of the carotid body in cluster headache

Dysfunction of the chemoreceptors of the carotid body in cluster headache was proposed by Kudrow (Kudrow, 1983). The hypothesis was based upon the observations that cluster headache attacks occurred in association with high altitude, during REM sleep (as detailed above) and following vasodilators such as nitroglycerine (Ekbom, 1968), all of which lead to hypoxaemia. Furthermore oxygen inhalation was successful at aborting acute attacks (Fogan, 1985). The theory suggested that the pathways concerned with cyclic cluster periods may begin centrally in the hypothalamus. The major influence of this physiological change was an inhibition of the sympathetic and disinhibition of parasympathetic supplies to the carotid body resulting in diminished peripheral chemoreceptor activity. The pathway concerned, with onset of spontaneous or induced attacks, was thought to be precipitated by oxygen desaturation. At a certain threshold this was proposed to induce a hyperactive chemoreceptor response (thought to be due to denervation supersensitivity) which stimulated the nuclei of the 7th and 10th cranial nerves and the respiratory centre. It was suggested that the pain, the autonomic features and vasodilatation associated with the attacks were all mediated by the 7th cranial nerve - a hypothalamically driven autonomic discharge via the greater

superficial petrosal nerve and pain via fibres carried in the nervus intermedius some of which branch off in the greater superficial petrosal nerve. The attacks were thought to spontaneously cease following elevation of PO_2 and a lowering of PCO_2 from stimulation of the respiratory centre, and from simultaneous exhaustion of receptor transmitters, stimulated by the 7th and 10th cranial nerves.

There are a number of unexplained discrepancies in this hypothesis. Kudrow conducted a study in 10 individuals with ECH in the active bout, 10 out of the active bout and in 5 controls. The study reports that oxygen saturation dropped in all three groups after administration of sublingual GTN, but decreased further significantly in the active group culminating in a cluster headache attack, while oxygen saturation returned to baseline levels in the control and remission groups. However mean oxygen saturation dropped from a baseline of 96.93% to 95.52%, the latter culminating in an attack (remission- 96.13% to 95.51%, controls 95.88% to 96.06%). First, the statistical analysis used was not discussed. Secondly the study results infer that quite marked sensitivity to subtle changes in PO_2 must exist in patients during the active bout if this is the mechanism for precipitation of acute attacks of cluster headache. Hyperventilation in association with spontaneous cessation of attacks has not been shown. Day time oxygen saturation associated with spontaneous attacks has not been adequately addressed. There is not a preponderance of patients with cluster headache who have chronic respiratory disease (Kudrow, 1980). The studies addressing sleep apnoea are small and it is not possible to conclude from this that sleep apnoea is a particular feature of cluster headache (Dexter, 1984; Kudrow *et al.*, 1984; Mathew & Frost, 1984). Nocturnal cluster headache attacks are not consistently preceded by oxygen desaturation in the small number of patients studied (Kudrow *et al.*, 1984), nor does induced oxygen desaturation (to 75%) trigger cluster headache attacks during the day

time (Zhao *et al.*, 1990). The hypothesis also implies that there is no involvement of the trigeminal nerve in the perception of the pain.

CHAPTER 4

Treatment of Cluster Headache

4.1 Introduction

The course of cluster headache does not seem to be influenced by hormonal, psychological, or social factors, apart from alcohol avoidance during the bout. Treatment has therefore been aimed at effective prophylaxis and rapid abortive therapy for the acute attacks. Small open and uncontrolled studies are due to the rarity and severity of the syndrome. In addition cautious interpretation of treatment trials arises from the potentially rapid spontaneous resolution of the attacks and cyclical nature of cluster headache. The mechanism of action of the majority of the treatments remains unknown. This aspect of drug treatment has not been addressed in this chapter.

4.2 Acute attack treatment

4.2.1 Subcutaneous sumatriptan

The most effective acute attack treatment is the sumatriptan subcutaneous injection. The efficacy has been evaluated in a randomised double-blind placebo-controlled crossover study involving 39 patients; 56% suffered from episodic cluster headache and 44% from chronic cluster headache (Ekbom & The Sumatriptan Cluster Headache Study Group, 1991). Six milligrams subcutaneous sumatriptan was compared with placebo across two cluster attacks. Successful relief of headache from very severe, severe or moderate pain to mild or none within 15 minutes of treatment was achieved in 74% of attacks compared to 26% treated with placebo ($p<0.001$). Forty-six percent of patients were pain free at 15 minutes after treatment with sumatriptan compared with 10% treated with placebo ($p<0.001$); 36% were pain free at 10 minutes after sumatriptan compared to 3% after placebo. The incidence of ipsilateral autonomic features was

reduced significantly after treatment with sumatriptan compared to placebo. Sumatriptan was well tolerated; the most common side-effects were injection site reactions, dizziness, tiredness, paraesthesia, numb hands, cold and hot sensations and a feeling of facial weakness.

In a subsequent dose-defining study 134 patients were randomised to receive two of three subcutaneous treatments – 6mg sumatriptan, 12mg sumatriptan or placebo (Ekblom *et al.*, 1993). Headache response from moderately severe pain or greater to mild or none at 15 minutes was achieved in 75% of patients with sumatriptan 6mg (n=92), 80% with sumatriptan 12mg (n=88) compared to 35% with placebo. The adverse event profile for the 12mg dose was greater (45%) than for the 6mg dose (34%). No electrocardiographic changes were noted after the treatments. Considering only a modest improvement was gained by use of the 12mg dose compared to 6mg and the greater incidence of adverse events associated with the higher dose the 6mg injection has been recommended for the treatment of acute attacks of cluster headache. In two small Japanese studies cited in a review of Sumatriptan (Plosker & McTavish, 1994) 3mg appeared to be equally effective as 6mg for the treatment of the acute attack.

A one-year open study reported successful treatment (as defined above) with 6mg subcutaneous sumatriptan of 88% of 2031 attacks in 52 patients (71% of the original 57 patients recruited had episodic and 29% had chronic cluster headache); 57% of patients were pain-free at 15 minutes (Gobel *et al.*, 1998). The overall efficacy of sumatriptan in patients with chronic cluster headache was 8% lower than that in patients with episodic cluster headache. The daily maximum dose of sumatriptan was 12mg, ie two injections in 24 hours and the number of attacks treated ranged between 2 and 182 per patient. The study reported neither tachyphylaxis nor loss of efficacy ‘in the long term’, although

details of the patient group, in terms of the range of duration of bouts of cluster headache and the average number of daily attacks treated during this time, were not given. This is important since most patients suffered from episodic cluster headache and by definition only patients with chronic cluster headache experience 'bouts' for one year or more (Headache Classification Committee of the International Headache Society, 1988). Therefore the duration of the term of the study was probably misleading. There *is* a case report of a 32 year old man with chronic cluster headache who received a total of 480 injections of 6mg subcutaneous sumatriptan over an 11 month period (Ekbohm *et al.*, 1992). More than 90% of the attacks resolved within 10 minutes (average 6.8 ± 3.4 minutes); the average duration of 61 attacks over the same period of time treated with analgesics or oxygen inhalation was 56.1 ± 20.8 minutes. There was no evidence of tachyphylaxis nor of a serious adverse event. Serial electrocardiograms during that period of time were normal.

Although an effective abortive agent sumatriptan does not prevent attacks of cluster headache when taken pre-emptively. This was shown in a placebo controlled parallel – group study involving 169 patients over a 1 week period during which patients were treated with sumatriptan 100mg orally eight hourly. In comparison to an established frequency and severity of attacks a reduction in attack frequency of 50% or more occurred in 23% of patients on sumatriptan compared with 22% on placebo (Monstad, 1995). However there has been an interesting case report of a patient with resistant CCH whose attack resolved with prophylactic treatment with Naratriptan 2.5 mg bd (Eekers & Koehler, 2001).

4.2.2 Intranasal sumatriptan

There have been two studies evaluating the benefit of sumatriptan intranasal spray. The

first study was open, involving 26 patients, 23 with episodic and 3 with chronic cluster headache (Hardebo & Dahlof, 1998). Four consecutive attacks were treated alternately with the nasal spray and the subcutaneous injection. The end-point used was reduction of pain from moderate or greater to none or background pain at 15 minutes. All attacks had to be treated within 5 minutes of onset at the defined severity which in practical terms may have been too strict. Complete pain relief followed subcutaneous sumatriptan in 49/52 of treated attacks while 7/52 attacks treated with the nasal spray gave complete relief with a total of 25/52 giving partial or complete pain relief. The study design was suboptimal and sample group small, demanding future controlled studies of intranasal sumatriptan adequately powered with regard to size and with clear end-points.

In a multicentre international randomised placebo-controlled study of intranasal sumatriptan patients treated one attack with sumatriptan and another with placebo. The primary end-point was headache response from very severe, severe or moderate to mild or none at 30 mins. A total of 118 patients were recruited (97 M 21F) 81 of whom provided data on the treatment of two attacks and 87 on one at least one attack (van Vliet *et al.*, 2001). For the first attack the placebo response rate was 30% (11/37) and the sumatriptan 20mg response rate 58% (29/50); for the second attack the rates were 33% (15/45) and 50% (18/36), respectively. In the overall analysis sumatriptan 20mg was statistically superior to placebo.

4.2.3 Oral Zolmitriptan

A multi-centre, double-blind, randomised, 3-period, cross-over, outpatient, study evaluated the efficacy of zolmitriptan 5 mg and zolmitriptan 10 mg orally with placebo (Bahra *et al.*, 2000). The primary efficacy parameter was pain reduction from very

severe, severe, or moderate to mild or one at 30 minutes. A total of 124 patients took at least one dose of study medication with 73% having episodic and 27% chronic cluster headache. For the primary endpoint, there was a statistically significant treatment-by-cluster-headache-type interaction ($p=0.0453$). Therefore, results are presented separately for episodic and chronic cluster headache. In patients with episodic cluster headache, the difference between zolmitriptan 10 mg and placebo at 30 minutes reached statistical significance (47% vs 29%; $p=0.02$). Mild or no pain at 30 minutes was reported by 60%, 57% and 42% patients treated with zolmitriptan 10 mg, zolmitriptan 5 mg and placebo, respectively (both $p\leq 0.01$ vs placebo). In patients with chronic cluster headache, response rates following zolmitriptan 5 mg or 10 mg were not significantly different from placebo at any endpoint. Both doses were well tolerated.

4.2.4 Oxygen Therapy

Oxygen therapy is an effective and safe treatment for acute cluster headache attacks. There is one double-blind placebo controlled cross-over study which has assessed the efficacy of oxygen as an abortive agent (Fogan, 1985). Nineteen patients with cluster headache defined by the Ad Hoc Committee on Classification of Headache (Ad Hoc Committee on the Classification of Headache, 1962) were included in the study. The patients were asked to treat up to 6 attacks with oxygen and 6 with air at 6 litres/minute via a non-rebreathing face mask for at least 15 minutes. Each treatment was started at the onset of a cluster attack. The response was scored as no (0), slight (1), substantial (2) or complete (3) relief. The score was averaged over all headaches for each treatment group to give a summary score. Two patients were mistakenly given the same gas twice. Fifty-six percent of 16 patients who treated their attacks with oxygen (1-5 attacks per patient/one treated 9 attacks with oxygen and none with air) experienced complete or substantial relief in at least 80% of the attacks. Seven percent of 14 patients who

treated their attacks with air (1-5 attacks per patient/ one treated 10 attacks with air and none with oxygen) gained similar benefit. The average relief score in the oxygen group was 1.9 ± 0.2 (SEM) against 0.8 ± 0.2 in the air group. The difference was highly statistically significant.

The benefit of oxygen therapy was subsequently shown in an open study involving 52 patients (33 with episodic and 19 with chronic cluster headache) who treated 10 attacks acutely with 100% oxygen at 7 litres/minute for 15 minutes. 'Treatment success' was defined as complete or almost complete cessation of pain within 15 minutes for at least 7 of the 10 attacks. Seventy-five percent of patients achieved treatment success. Sixty-two percent of responders had aborted their attacks within 7 minutes and 93% within 10 minutes. A greater proportion of episodic cluster headache sufferers responded (79%) compared to the chronic cluster headache group (68%) (Kudrow, 1981).

The main restriction to the use of oxygen in the United Kingdom is the availability of the regulator required to provide patients with the flow rate of oxygen recommended by the aforementioned studies. These are not available on prescription and must be financed by the patient at a cost of about £150.00. The equipment available through the current National Health Service provides a maximum flow rate of 4 litres/minute.

The benefit of hyperbaric oxygen (HBO) was reported in a patient with a 26 year history of episodic cluster headache who was suffering from a bout which had lasted 21 months, and who had proven to be resistant to a number of medical therapies including high flow oxygen and surgical procedures. She had been experiencing 3-5 attacks each week lasting between 45 minutes and 4 hours. Twenty minutes into an attack and after 5 minutes of receiving 100% oxygen at 2 atmospheres the attack resolved completely.

The attacks recurred 2.5 hours later and again three days later. Thereafter on reporting she had been attack-free for 7 months (Weiss, 1989).

Twelve patients with episodic and two with chronic cluster headache who had been refractory to treatment with 100% oxygen at 7l/min for 15 minutes had a total of 18 attacks (12 nitroglycerine provoked and 6 spontaneous) treated with HBO as above. All achieved complete relief within a mean of 6.2 minutes (range 30s – 13 minutes) (Porta *et al.*, 1991).

There has been one double-blind placebo controlled study of 13 patients with episodic cluster headache. Seven were treated with HBO and 6 with placebo. The attack was aborted in six of the 7 treated with HBO from 5 to 13 minutes after the onset of treatment whilst none on placebo showed a change in attack duration. During the 2 month follow up period in 3 patients treated with HBO the bout stopped whilst in the 3 others no attack occurred for a period of 4-6 days before reverting to the pre-treatment pattern. In the patients who had received placebo the attack remained unmodified (Di Sabato *et al.*, 1993).

Although HBO treatment in the small number of patients studied appears to be efficacious in treating acute attacks, as an abortive treatment it is not a practical option and is expensive. However, such a treatment would be worthwhile if it were truly capable of terminating a bout prematurely. This was assessed in 4 patients with chronic cluster headache (for 3-15 years). Each patient kept a 2 week daily headache diary prior to a 2 week course of 7 times daily 70 minute sessions breathing 100% oxygen in the HBO chamber at 2.5 atmospheres. A daily headache diary was kept during this time and for a 2 month follow-up period. One patient's attacks stopped during HBO treatment

which was stopped after 8 days due to ear dysbarism; this patients had no further attacks for 31 days with a baseline frequency of 3 attacks/day prior to HBO therapy. Patient 2 experienced a reduction in frequency (2 / day to once every 3 days) and duration of attacks (60 to 30 minutes) with recurrence of the original pattern of symptoms two days after cessation of treatment. The 2 week course was repeated with an identical response the second time. The third patient's attacks reduced by half in frequency for the duration of the treatment only. The fourth patient did not benefit from the treatment at all. Thus this study suggests HBO therapy to be beneficial in reducing the duration and frequency of attacks of cluster headache in patients resistant to other prophylactic agents, but its role in prevention is transient at best.

4.2.5 Ergotamine

Prior to the advent of sumatriptan, ergotamine derivatives were the most widely used symptomatic treatment for cluster headache. Although there has been no comparative study of the different routes of administration clinical experience recommends parenteral treatment as the most effective. The use of the oral, rectal, sublingual and inhaled preparations have also been reported to be effective (Duvoisin *et al.*, 1961). Friedman and Mikropoulos administered ergotamine derivatives orally, by suppository or injection in an open fashion in 35 patients (Friedman & Mikropoulos, 1958). All 'proved to be effective to a greater or lesser extent in 85%..... the best results were obtained when ergotamine or dihydroergotamine (DHE) was used parenterally.....the use of cafergot suppositories proved to be more effective than when used by mouth and more rapid in its action'. Kudrow reported in his series of 100 patients that 79% obtained relief from the sublingual or inhaled preparations of ergotamine (Kudrow, 1980). In a double blind placebo-controlled trial of DHE in 22 patients. 133 attacks were treated with placebo and 137 with DHE (Andersson, 1986). The effect of DHE

was significantly better than placebo ($p < 0.05$); there was no change in attack frequency or duration. However the use of ergotamine derivatives is limited by the poor bioavailability of the oral and rectal preparations (Bulow *et al.*, 1986; Ekbom *et al.*, 1983 ; Ekbom *et al.*, 1981), the adverse event profile (Silberstein & Young, 1995) and restricted availability in the United Kingdom of the parenteral and inhaled formulations.

4.2.6 Intranasal lignocaine and cocaine

An 80% or greater improvement of nitroglycerine induced cluster headache was reported in 9 of 10 patients following the application of cocaine (50 mg cocaine hydrochloride flakes on a cotton swab) to the region of the pterygopalatine foramen ipsilateral to the side of the headache; the improvement occurred within 3 minutes of treatment (Barre, 1982). A 70-90% abortion rate of spontaneous attacks was subsequently observed with a 5-10% intranasal solution of cocaine over a 1-2 week period in 9 of 11 patients. One patient who exceeded the recommended application rate (25-35mg cocaine 1-2 times within four hours) noted a mild central nervous system excitation with inability to return to sleep for three hours. Eleven patients participated in the study; 2 had chronic and 9 episodic cluster headache. Information regarding whether the non-responders suffered from chronic or episodic cluster headache was not given. The usual average attack duration across the patients had been between 20-180 minutes.

Application of intranasal lignocaine to the pterygopalatine ganglion has also been shown to be effective without the potential for addiction and tachyphylaxis which may accompany the benefit obtained by the similar application of cocaine (Kitrelle *et al.*, 1985). Seventy-five to one hundred percent relief was obtained in 4 of 5 patients (2 with chronic and 3 with episodic cluster headache) with nitroglycerine induced cluster headache attacks within 3 minutes after application of 1ml 4% intranasal lignocaine

ipsilateral to the pain (preceded by a few drops of 0.5% phenylephrine hydrochloride to facilitate decongestion). The average attack duration across patients had been between 45 and 180 minutes. The non-responder suffered from episodic cluster headache and had also failed to respond to intranasal cocaine. Three patients subsequently reported 90-100% relief of spontaneous attacks over a 2 –13 month period; the average time to abortion of the attacks was not given.

An open study of 24 patients showed the benefit of 0.5-0.8ml 4% intranasal lignocaine in 8 of 12 patients, of 0.3ml 10% intranasal cocaine in 4 of 5 patients and 5 of 6 patients treated with a solution of both (Hardebo & Elner, 1987). In 11 of the patients the sympathomimetic agent xylometazoline hydrochloride (0.4-0.8 ml of a 0.1% solution) was used either alone or together with the anesthetics. The agent alone was ineffective in reducing the pain but effective in reducing nasal congestion, and did not improve pain when used in combination with either cocaine or lignocaine except in 3 patients when administered before the use of an anaesthetic agent. Patients were assessed over a 2 week period having experienced at least one attack a day in the immediately preceding period. There was no placebo arm to the study, the end points used to assess efficacy are not adequately detailed and efficacy was assessed by questioning the patients after the course of treatment by the examiner. The comment was made that when the treatments were effective, both pain and autonomic symptoms were maximally reduced within ½ min (in 3 patients within 5 min), provided the agents were administered early in the course of an attack (within about 5 min after the start of symptoms).

However another open study of 30 patients treated with intranasal lignocaine across two attacks using a 10 minute endpoint, none obtained 60-100% relief, 8 obtained 40-60%

relief, 8 20-40% relief and 14 0-20% relief (Robbins, 1995).

There has been one double blind placebo-controlled study which addressed the efficacy of 10% cocaine hydrochloride and 10% lignocaine administered to the region of the pterygopalatine fossa under anterior rhinoscopy in 9 (2 ECH 7 CCH) patients with cluster headache during GTN-induced attacks (Costa *et al.*, 2000). A significant response to both agents was observed ($p < 0.01$ for both treatments). The study provides a pilot for future studies of spontaneous attacks and self administration of the treatments.

Intranasal lignocaine may provide an alternative effective acute treatment in patients experiencing multiple cluster headache attacks who do not have access to oxygen therapy and in whom the use of the sumatriptan subcutaneous injection is restricted to twice a day, whilst suitable preventative therapy is being established. The problem of adequate self-administration with intranasal preparations exists and such therapies are therefore not commonly used.

4.3 Preventative treatment

4.3.1 Calcium channel blockers

The use of calcium channel blockers in the treatment of cluster headache was founded theoretically on their property of altering cerebrovascular resistance in a condition where the pathogenesis was thought primarily to be vascular in origin. The benefit of calcium channel blockers was first reported in 8 patients with chronic cluster headache in a double-blind cross-over two dose study of nimodipine (Meyer & Hardenberg, 1983). An open trial of 13 patients found nimodipine 120mg daily to be effective in 53% of patients all with ECH. A successful outcome was defined by cessation of

attacks within 7 days of starting treatment. Treatment was started within a week of starting a bout, the duration of which was greater than 20 days in 92% of patients. A successful outcome in successive bouts (n=3) was not maintained. The small number of patients in both the studies is noted (de Carolis *et al.*, 1987).

Subsequently in an open study, 48 patients (33 with episodic and 15 with chronic cluster headache) were treated with verapamil (Gabai & Spierings, 1989). The starting dose of 120mg bd was increased until the desired response was achieved or intolerable side effects developed. The episodic group received between 240-600mg daily and the chronic group between 120-1200mg daily. The primary end-point was a reduction in headache frequency. Nineteen percent obtained less than 25% improvement, 12% between 25 and 75% improvement and 69% more than 75% improvement. The difference in response rate between the episodic and chronic cluster headache group was not statistically significant. The range of duration of the bouts in the episodic group was not given. Initiation of treatment varied between 1-32 weeks into the bout (average 6.5 weeks) which therefore may have influenced the result. Of the 9 (19%) patients who gained least benefit, 3 discontinued treatment due to adverse effects (bradycardia, abdominal cramps, nausea and vomiting) all at 240mg. Tolerable side effects included constipation, drowsiness, depression, bad taste/smell and pedal oedema.

A double-dummy, double-blind crossover comparison of lithium and verapamil in cluster headache prophylaxis was performed in 30 patients with cluster headache over a period of 23 weeks. This comprised a 2 week placebo run-in period, followed by an 8 week period on either verapamil 360mg or lithium 900mg daily. This was followed by a 2 week placebo washout period then patients who had received verapamil initially were crossed over to receive lithium and vice versa. Finally a three week placebo wash-out

period completed the study. A statistically significant reduction of both analgesic consumption and headache index (based on headache frequency, severity and duration) was seen with both drugs compared to placebo. Although a greater reduction was seen in the first week with verapamil, the lithium levels were subtherapeutic. Verapamil was better tolerated (Bussone *et al.*, 1990).

There has been only one placebo-controlled parallel study of verapamil (Leone *et al.*, 2000). Fifteen patients each, with ECH of duration at least 20 days, were randomised to receive either verapamil 120mg tds or placebo for 14 days after a 5 day run-in period. The primary end point was a 50% reduction in attack frequency. Eighty percent in the verapamil arm responded while none in the placebo group responded. Forty percent responded in the first week and the other forty in the second week ($p < 0.001$ for the total group second week response). During the second week 27% became pain free. Twenty percent did not respond.

4.3.2 Lithium

The introduction of lithium in the prophylaxis of cluster headache was largely based upon the cyclical nature of the syndrome and the efficacy of the drug in the treatment of another cyclical disorder, manic-depressive psychosis. The benefit of lithium in the treatment of cluster headache was first reported in 1977 (Ekbom, 1977). Numerous studies subsequently showed the prophylactic benefit of lithium in both episodic and chronic cluster headache (Damasio & Lyon, 1980; Klimek *et al.*, 1979; Kudrow, 1977; Mathew, 1978; Medina *et al.*, 1978; Savoldi *et al.*, 1983); one study however showed benefit in chronic cluster headache but not in episodic cluster headache (Ekbom, 1981). Notably the studies were small (between 7 and 32 patients), open, uncontrolled and the parameters used for the primary end-point varied or were not detailed. The largest study

performed (Manzoni *et al.*, 1983a) included 90 patients (68 with episodic and 22 with chronic cluster headache). Lithium carbonate 900mg daily (in some cases 600 or 1200mg) was used with plasma levels of 0.3-0.7meqv/L. A headache index ratio was used to compare pre- and post-treatment periods of equal length. In the episodic group three-quarters of patients showed an improvement of >60%. This improvement was not maintained with during treatment of successive bouts in a subgroup of patients. Three patients with episodic cluster headache and frequent bouts were treated continuously with lithium for a year and remained attack-free; however on discontinuation of the drug the attacks returned within 1-3 weeks. In the chronic group 11 of 22 showed consistent improvement both in the short and long term (follow-up period 9-48 months). In 7 of the 22 patients, lithium treatment provided excellent results initially but was later followed by some transient worsening; in the remaining 4 only partial benefits were observed initially and treatment proved less effective after a few months. The initial benefit of lithium therapy was observed within 2 weeks of starting treatment. The effects of cessation of lithium administration after at least five months of continuous treatment was studied in 9 cases. In 6 the attacks re-appeared immediately and in 3 the attacks recurred after pain-free intervals of four to six months. The development of episodic cluster headache in the latter group needs to be borne in mind. Mild adverse effects included tremor, thirst, insomnia, diarrhoea, lethargy and euthyroid goitre. Abdominal pain, nausea, vomiting, light-headedness, poor concentration and confusion have also been reported (Kudrow, 1977; Mathew, 1978). Headaches attributed to lithium therapy itself have been reported in patients with cluster headache (Alvarez-Cermeno *et al.*, 1989; Brainin & Eisenstadter, 1985; Kudrow, 1977).

More recently the benefit of lithium prophylaxis over placebo in episodic cluster headache was not proven in a placebo-controlled parallel study of 28 (Steiner *et al.*,

1997). However this may be attributed to the restrictive study design of a one week trial period of single daily dosing of 800mg lithium carbonate or placebo, with cessation of attacks as the primary end-point.

4.3.3 Corticosteroids

Despite earlier reports that suggested cortisone was not effective in the treatment of cluster headache (Friedman & Mikropoulos, 1958) the efficacy of corticosteroids was established in a double-blind placebo-controlled trial of 19 patients who had been resistant to methysergide and ergotamine (Jammes, 1975). Seventeen of the 19 gained benefit from a single dose of prednisone 30mg whilst no improvement was gained with placebo. In a series of 77 patients with episodic cluster headache who had been unresponsive to methysergide, prednisone therapy resulted in marked relief in 77%, partial relief in 12% and no relief in 12% (Kudrow, 1980). Forty percent of 15 chronic cluster headache patients obtained marked improvement whilst 33% gained partial improvement. The dose regimen used was 40mg for five days followed by tapering of the dose over 2 –3 weeks. The comment was made that as the dose is reduced to 15mg/day the addition of ergotamine may be required, suggesting that as the dose is decreased the attacks return.

A retrospective study reported the treatment of 19 cluster headache patients with a peak dose of prednisone 10-80mg /day; the peak dose was maintained for 3-10 days after which the dose was tapered off (Couch & Ziegler, 1978). Although 10 patients were given the diagnosis of chronic cluster headache this was loosely defined as ‘cluster headache at a steady frequency and in a pattern devoid of cyclical variation over a period of at least three months’. Fourteen of the 19 patients (73%) had greater than 50% relief and 11 (58%) had 100% relief from headache. The remaining 5 patients had less

than 50% improvement. The peak dose related to response suggested that an initial dose of at least 40mg daily was required for a beneficial effect. Recurrence of symptoms occurred in 9 of 11 patients who were followed-up as the dose was tapered to 10-20mg daily.

4.3.4. Methysergide

The benefit of methysergide in the prophylactic treatment of migraine and cluster headache has been reported since late in the 1950s. Curran and colleagues reported upon a total of almost 500 patients from 16 studies with cluster headache treated with methysergide between 4 and 16mg daily; about three quarters showed an improvement (Curran *et al.*, 1967). The report included a study by Lovshin on a large series of 159 patients started on 8mg methysergide daily for cluster headache, the dose was increased up to 16mg daily. Five patients had to stop treatment, 3 due to gastrointestinal side effects and 2 due to exacerbation of existing coronary heart disease; 6 other patients with known coronary heart disease were treated without ill effect. Doses in these patients were not given. One hundred and twenty three patients showed an improvement. Twenty-six patients were treated for two bouts and 6 for three; the effect was shown to be consistent in some patients across successive bouts (Lovshin, 1963) but a declining benefit has been observed in others (Kudrow, 1980; Lovshin, 1963). Kudrow reported the benefit of methysergide in patients with episodic cluster headache but not in chronic cluster headache (Kudrow, 1980). Krabbe treated 42 patients prospectively (16 with episodic symptoms) for 6 months in doses ranging between 1 and 12mg. Twenty-six percent reported good to excellent responses and good tolerance; no difference between patients with episodic and chronic symptoms was reported (Krabbe, 1989). Graham reported retrospectively on five-hundred patients with various types of headache treated with methysergide (Graham, 1964). Twenty percent reported

side-effects necessitating withdrawal of the drug. The most common included nausea, vomiting, indigestion, weight gain, peripheral oedema, cold extremities, depression and dizziness. Occasional patients reported peripheral vascular insufficiency in doses as small as 1mg whilst others showed none with 30mg/day. Coronary insufficiency was reported in 4 patients. This was the first report of retroperitoneal fibrosis associated with the use of methysergide, in two patients. A total of 27 patients was published in a subsequent report 2 years later (Graham *et al.*, 1966) and fibrosis of cardiorespiratory structures shortly thereafter (Graham *et al.*, 1967). The minimum dose used was 2mg daily. The shortest duration of treatment prior to symptom onset was 6 months. The phenomenon did not seem to be a dose related response. Cessation of therapy resulted in partial or complete improvement of symptoms, signs and X-ray evidence of disease in all patients. Those treated by drug withdrawal fared equally well as those in whom surgical measures were employed, even though the degree of involvement was more severe. Improvement in symptoms and signs occurred within a few days. Recrudescence occurred when the drug was taken again.

There has been no placebo-controlled randomised double-blind study evaluating the benefit of methysergide in the treatment of cluster headache.

4.3.5 Ergotamine

The prophylactic effect of ergotamine in the treatment of cluster headache was first reported by Ekbom in 13 of 16 patients using ergotamine tartrate 2mg 2 to 3 times a day (Ekbom, 1947). Friedman and Mikropoulos (Friedman & Mikropoulos, 1958) reported the use of ergotamine preparations by mouth, rectally or parenterally to be effective at preventing nocturnal attacks of cluster headache which was supported by Duvoisin (Duvoisin *et al.*, 1961).

4.3.6 Pizotifen

There has been a single study which evaluated the benefit of pizotifen in 28 patients. Patients with an anticipated period of at least a month were included. There were four periods each of 5 days during which the dose was gradually increased starting with a 5 day placebo period. During the final period the dose was tailored to the patients' tolerance and response. The maintenance dose range was 1-4mg daily and was continued afterwards; most patients required a daily dose of 2-3mg. The total period of treatment covered 4-12 weeks. Six patients became pain free, although 5 continued to experience mild twinges of pain which did not develop into attacks suggesting the attacks to be suppressed rather than the bout to have ceased. Ten patients experienced greater than 50% improvement of frequency or severity. Ten gained no improvement; two of these patients withdrew from side effects of drowsiness and anxiety. Two came out of their bout during the placebo period and subsequent treatment. Thus the study suggests that pizotifen may be beneficial as a prophylactic agent in the treatment of cluster headache (Ekbom, 1969).

4.3.7 Sodium Valproate

Gamma-aminobutyric acid (GABA) is present in the small interneurons of the suprachiasmatic nucleus which is important in circadian time-keeping. Sodium valproate potentiates the levels of GABA in the brain. This property and its benefit in the treatment of manic-depression prompted the use of sodium valproate in the treatment of cluster headache. The efficacy of sodium valproate in cluster headache has been assessed in an open pilot study of 15 patients (13 with episodic and 2 with chronic cluster headache). In most of the patients with episodic disease treatment was started early into the bout and treatment continued to the expected end of the bout. Doses

between 600-2000mg daily were used. Complete relief from attacks was observed in 9 patients within 1 week and partial relief observed in 2 patients. No correlation was found between sodium valproate levels and efficacy. No serious adverse events were reported apart from mild nausea (Hering & Kuritzky, 1992).

4.3.8 Other prophylactic agents

There has been a single open study of 9 patients with cluster headache 2CCH and 7 ECH) and one with cluster-tic syndrome all of whom were reported to respond to Topiramate 50-125mg daily. All responded within 1-3 weeks. However of those with ECH 5 should have been due to come out of active bout at the time of response therefore the result is difficult to interpret in these patients (Wheeler & Carrazana, 1999). In a study of 8 patients with ECH and 4 with CCH Gabapentin 900mg daily stopped all attacks within 8 days of starting treatment (started within one week of onset in ECH). The results are encouraging and the longer term responses in these patients would have been interesting (Leandri *et al.*, 2001). In a pilot study of 9 patients (3 defined as CCH; 2 had bouts less and up to 12 months in duration) treated with baclofen 15-30 mg, six reported cessation of attacks within a week, one was substantially better and attack free by week 2, and two deteriorated and required alternative treatment (Hering-Hanit & Gadoth, 2000). The follow-up period was 18 months. One patient may have had spontaneous resolution of the bout based upon usual bout duration.

4.4 Surgical Treatment

4.4.1 Introduction

In view of the spontaneous remissions in cluster headache surgical treatment has been reserved for patients with chronic symptoms refractory to medical therapy. Procedures have been aimed at interrupting the nociceptive pathways considered pertinent or the

parasympathetic pathways. The most successful surgical treatments have been aimed at the trigeminal nerve or ganglion, and to a lesser extent the pterygopalatine ganglion, the nervus intermedius and the greater superficial petrosal nerve. A number of alternative procedures have been less successful but notably the numbers of patients studied has been small. These include resection of the ipsilateral superficial temporal artery (Watson *et al.*, 1983), supra- and infra-orbital nerve blockades and avulsions (Stowell, 1970; Watson *et al.*, 1983), decompression of the facial nerve (Solomon & Apfelbaum, 1986), occipital nerve (Anthony, 1987) and transection of the spinal trigeminal tract (Sweet, 1988). Surgical procedures should be considered with caution; individuals who give a past history of attacks on the opposite side may develop symptoms on this side following a successful surgical procedure to the usually symptomatic side (Lance & Goadsby, 1998; Onofrio & Campbell, 1986). The following reports are of procedures in patients with chronic cluster headache unless otherwise stated.

4.4.2 Trigeminal ganglion

Maxwell treated 8 carefully selected patients based upon severity, unilaterality and chronicity of symptoms (Maxwell, 1982). A trigeminal lignocaine blockade pre-operatively resulted in complete anaesthesia in the distribution of the ipsilateral trigeminal nerve with absence of corneal reflex. Five patients were pain free for 7-59 months. Two had occasional mild headaches at 25 and 12 months not requiring treatment. In one patient the pattern reverted from chronic to episodic cluster headache. Most interestingly in one of the completely pain-free patients, a pattern of hemifacial flushing, lacrimation, and nasal congestion persisted. Watson and colleagues reported on 27 radiofrequency lesions of the trigeminal ganglion on 13 patients with chronic cluster headache (Watson *et al.*, 1983). All patients had symptoms for at least one year without remission. One patient may have suffered from chronic paroxysmal hemicrania

with inadequate doses of indomethacin tried. Twelve procedures resulted in pain relief of at least 5 months (range 5-36 months; median 24 months). Success was associated with anaesthesia in the area most affected by pain. One patient developed anaesthesia dolorosa and another transient CSF rhinorrhea. Onofrio and Campbell reported on 16 radiofrequency lesions of the trigeminal ganglion (Onofrio & Campbell, 1986). Eight patients had 'excellent' results (12-32 month remission), 2 'good', 2 'fair' and 4 poor results. Thirteen of the patients had corneal anaesthesia and one corneal numbness. Three patients had corneal anaesthesia without pain-relief. Mathew and Hurt (Mathew & Hurt, 1988) treated 27 patients with percutaneous radiofrequency trigeminal gangliorhizolysis. The follow-up time ranged between 6-63 months. Fifteen patients had excellent results, 2 very good, 3 good, 1 fair and 6 poor. Those with excellent results had V₁ and V₂ analgesia with reduction of the corneal reflex. Complications were mild but included anaesthesia dolorosa and corneal infection. In a prospective study of 18 patients with CCH (mean follow-up 5.2 years) percutaneous retrogasserian glycerol rhizolysis was concluded to be safer but less efficacious than radiofrequency retrogasserian rhizotomy (Pieper *et al.*, 2000). Repeated procedures can be performed. A high 'lost to follow-up' rate was noted.

4.4.3 Trigeminal nerve

Watson and colleagues performed trigeminal sensory root section in eight patients (Watson *et al.*, 1983). Good results were obtained in 5 of 9 procedures, with relief from 24 months to 8 years, median 44 months. These results were associated with retro-Gasserian lesions and anaesthesia in the main pain site. One patient suffered from anaesthesia dolorosa post-operatively and another from neurogenic keratitis and glaucoma. Sensory rhizotomy resulted in one excellent result (55 month remission) and 3 poor results reported by Onofrio and Campbell (Onofrio & Campbell, 1986); 5

excellent and 1 poor result occurred in patients who underwent rhizotomy after failed radiofrequency procedures of the trigeminal ganglion. Sweet reported on 28 radiofrequency trigeminal rhizotomy procedures in 20 patients (Sweet, 1988). He advocated a response to pre-operative retrogasserian lignocaine blockade (performed in all the patients) and severity of sensory loss after surgery to be predictive of a successful result of trigeminal rhizotomy based on the premise that pain relief indicates that the major pain pathway is through the trigeminal system and that surgery affecting the trigeminal system may be beneficial. This was supported by a response in 13 of the 20 patients to trigeminal rhizotomy. Eleven followed post-operatively for an average of 5.3 years (10 months to 20 years) were pain-free, although 4 required supplemental medication; two developed recurrence at 8 and 10 years post-operatively. Long-term results of radiofrequency rhizotomy in 7 patients were reported by Taha and Tew (Taha & Tew, 1995). All patients had post-operative sensory loss in the distribution of the first and second divisions of the trigeminal nerve. Chronicity of symptoms ranged from 4 to 15 years. Two patients remained pain free 5 and 20 years later, in 3 mild pain recurred 6-12 months later (two were controlled with appropriate medication and one with simple analgesics), in two patients pain recurred at 4 days and two months after surgery. Five of the seven patients underwent successful pre-operative lignocaine blockade as advocated by Sweet (Sweet, 1988); of the 5, three had excellent or good results post-operatively and two had poor results. The extent of the analgesia induced by the procedure did not correlate with degree of success.

4.4.4 Pterygopalatine ganglion

Sixty-six patients, 56 with episodic cluster headache and 10 with chronic symptoms unresponsive to medical therapy underwent radiofrequency lesions of the pterygopalatine ganglion (Sanders & Zuurmond, 1997). Of the episodic group 61%

achieved complete pain relief and 14 no relief with a mean follow-up period of 29.1 ± 10.6 months. Unfortunately details of bout duration in those patients who obtained complete relief and time to complete relief, and of repeat lesioning in some, was not given. Of those patients with chronic cluster headache 30% obtained complete relief, 40% obtained no relief with mean a follow-up period of 24 ± 9.7 months. Temporary post-operative epistaxis was observed in 8 patients, cheek haematoma in 11, hyperaesthesia of the palate in 9 with complete resolution by 3 months and inadvertent partial radiofrequency lesioning of the maxillary nerve in four patients. Meyer and colleagues treated 13 patients unresponsive to medical therapy with pterygopalatine ganglionectomy (Meyer *et al.*, 1970) and in those who obtained an immediate response to local anaesthetic blockade of alcohol provoked attacks. They found seven patients no better, four improved, and two having no pain at all at one year. These patients mostly seemed to have ECH although with frequent short bouts.

4.4.5 Nervus Intermedius

The nervus intermedius is the sensory component of the facial nerve which also contains the parasympathetic fibres which branch off as the greater superficial petrosal nerve. Sachs reported the benefit of nervus intermedius section in 4 cases of chronic cluster headache relieved for up to 17 years; this was followed by two further successes and two failures (Sachs, 1969). The outcome of combined trigeminal and nervus intermedius procedures reported by Morgenlander and Wilkins was disappointing (Morgenlander & Wilkins, 1990). Rowed lesioned the nervus intermedius in 8 patients (Rowed, 1990). An intimate relationship between branches of the anterior inferior cerebellar artery and the nervus intermedius/VII nerve complex were found. In five of the patients there was delayed recurrence of symptoms from 2-4 months postoperatively, one experienced mild early postoperative recurrence for 10 days

followed by a 20 month remission period at reporting, 2 patients failed to gain improvement.

4.4.6 Greater superficial petrosal nerve

Benefit was reported by Gardner and colleagues in 1947 in 13 patients who underwent a total of 17 resections of the greater superficial petrosal nerve ipsilateral to the symptomatic side (Gardner *et al.*, 1947). Although ‘excellent’ results were reported in a quarter of cases, half had a fair response and the remainder were classed as failures. Stowell reported on 36 patients who underwent section of the greater superficial petrosal nerve over a 20 year period; 32 had complete relief ‘for a period of time’ while 4 had no relief (Stowell, 1970). Fifteen developed recurrence and of four who had repeat procedures 3 had complete relief. No further details regarding usual bout duration and period of relief post-operatively was given. Watson and colleagues (Watson *et al.*, 1983) summarised similar results in a number of studies of small number with remission periods varying from five months post-operatively, up to 14 years. Sweet sectioned the greater and lesser superficial petrosal nerves in 13 patients with ‘temporary or no relief ‘ in 8 patients and ‘full or good relief in 5’ varying from 6 to 27 months (Sweet, 1988). All 5 who obtained good relief subsequently suffered recurrence of symptoms. Based upon intra-operative stimulation experiments some authors concluded that the greater superficial petrosal nerve contains pain fibres and that relief occurs as a consequence of direct section of the pain pathways and not the interruption of a vasodilator efferent pathway (Watson *et al.*, 1983).

4.5 Summary

The most rapid abortive treatment for acute attacks of cluster headache is the sumatriptan subcutaneous injection. The safest most effective treatment is 100% high flow oxygen. Prophylactic treatment does not seem to alter the course of the disease (Manzoni *et al.*, 1983a; Savoldi *et al.*, 1983). Effective prophylaxis appears to suppress the attacks of cluster headache until natural remission occurs. The natural remissions of the syndrome place caution upon interpretation of studies showing efficacy of prophylactic treatments in episodic cluster headache. It may therefore be proffered that the most reliable efficacy data is obtained in studies involving patients with chronic cluster headache. However although clinical observation suggests that prophylactic therapy of chronic cluster headache is less satisfactory than for episodic cluster headache, this has not been formally proven since most study groups have been small with markedly disproportionate numbers of patients with chronic cluster headache to enable realistic statistical results. Lithium, corticosteroids, verapamil and methysergide have been shown to be effective prophylactic agents although neither lithium nor methysergide has supportive placebo-controlled trial data. Due to the spontaneous remissions of the disorder surgical treatment should be reserved for patients with chronic and strictly unilateral symptoms refractory to medical treatment. Procedures aimed at the trigeminal nerve and ganglion seem to produce the best results, but success has also been reported for procedures involving the pterygopalatine ganglion, the nervus intermedius and the greater superficial petrosal nerve.

CHAPTER 5

Functional Imaging in Head and Facial Pain

5.1 Functional imaging studies in migraine headache

5.1.1 Introduction

Most of the work with functional imaging in head pain has been done in patients with migraine. The International Headache Society criteria for migraine headaches are episodes of unilateral throbbing pain, of usually moderate or severe intensity which inhibit daily activities. The pain is exacerbated by movement and accompanied by nausea and/or vomiting, and sensitivity to light and sound. The episodes may occur with or without aura symptoms defined as idiopathic recurring symptoms unequivocally localisable to the cerebral cortex or brain stem, usually gradually developing over 5-20 minutes and lasting less than 60 minutes. The headache usually follows the aura symptoms within the hour (Headache Classification Committee of the International Headache Society, 1988). Migraine with aura occurs less commonly than that without aura, in about a third of sufferers (Russell *et al.*, 1995c). The one year prevalence of migraine is 18% in women and 7% in men (Steiner *et al.*, 1999). Aura symptoms are visual in the majority of patients. Visual aura symptoms include positive features (flashes, zig-zags, circles of light or rippling vision) and negative features (patchy scotomas, hemianopia, tunnel vision). About 10% of patients experience the classical progressive slow march of symptoms – fortification spectra which expand across the visual field, leaving behind a scintillating scotomatous defect. Other less common but typical aura symptoms include unilateral paraesthesia and/or numbness, unilateral weakness and disturbance of speech such as an aphasia (Ferrari, 1998).

In 1941 Lashley plotted his own visual scotoma in migraine and calculated that the visual cortex was being compromised by a process advancing at about 3mm/minute (Lashley, 1941). In 1944 Leao described cortical spreading depression in animals, a progressive shutdown of cortical function moving slowly over the cerebral cortex at a speed of 2-3mm/min; this lasted between 5-60 minutes before recovery and he speculated this to be related to the fortification spectra of migraine (Leao, 1944).

Perfusion has been used as an index of synaptic activity in the brain based on the established principle that cerebral blood flow and metabolism are tightly coupled (Frackowiak & Friston, 1994). The use of inhaled or injected (intravenous) xenon-133, a gamma-emitting radioisotope, for the measurement of cerebral blood flow has been well described (Olesen, 1991). Studies using intra-arterial xenon-133 have shown that localised changes in regional cerebral blood flow occur during different forms of stimulation, information processing and motor functions; these have shown that cortical processes were paralleled by corresponding changes in regional blood flow (Lassen *et al.*, 1977).

5.1.2 Xenon-133 with the use of stationary detectors and single photon positron emission tomography (SPECT) in migraine with aura

The earlier functional imaging studies were performed in patients with provoked and spontaneous attacks of migraine with aura using xenon-133 intracarotid angiography and inhaled xenon-133 and the use of stationary detectors. The procedure involved during carotid angiographic cerebral blood flow measurements was found to provoke attacks of migraine with aura in individuals with a history of migraine. The provoked attacks were similar to the patients' spontaneous attacks (Lauritzen *et al.*, 1983; Olsen *et al.*, 1987). The angiographic method involved repeated intracarotid boluses of

xenon-133 (usually injected just below the carotid siphon). The inhaled method involved inhalation of a Xenon-133-air mixture for about 1 minute until a steady state was achieved. Regional cerebral blood flow measurements were made from the detection of radioactivity by a camera with 254 stationary detectors over one hemisphere; earlier cameras comprised of 16 detectors. The measurement could be repeated at 10 minute intervals 4-6 times. Time-intensity curves were used to measure regional cerebral blood flow. Intensity values were obtained from the camera over different areas of the brain thus enabling regional cerebral blood flow values for different parts of the cerebral cortex to be obtained. A resting value was obtained for each area of the cerebral cortex and compared to a mean value (usually 50ml/100g/min). Alternatively differences between two different states were considered. The type of resolution gained with this type of method was 1-5cm² (1cm with a camera with 254 detectors and 5cm with 16 detectors). The arterial method, although invasive, has the advantages of avoiding extracerebral contamination, and eliminating interhemispheric cross-talk as as only one hemisphere is labelled (Olesen, 1991).

The use of gamma-emitting radioisotopes can also be used for tomographic imaging. Single photon emission computerised tomography measures the concentrations of radioactivity in tissue after the injection or inhalation of a chemical compound labelled with a single-photon-emitting isotope. The xenon-133 method involves intravenous or inhaled administration of xenon-133 and the use of a rapidly rotating tomographic device which enables dynamic tomographic recordings of the uptake and washout of xenon-133 from the brain to be made. Information is gained from 3 slices of the brain of about 2cm thickness at 10-20 minutes intervals; this is done 3-4 times over 1-1.5hrs. Cerebral blood flow measurements can then be made. The sensitivity of the

tomographic method is considerably greater than that of a gamma camera. Absorption in tissue of the weak gamma radiation does mean that deeper structures are poorly seen and blood flow changes are largely confined to the cortex. Although a number of tracers can be used with this technique to measure cerebral blood flow, xenon-133 has been most widely used in studies of head pain as it provides the most optimal combination of temporal and spatial resolution (although the latter is still about 1.7cm² at best) for investigating the symptoms of primary head pain syndromes. Xenon-133 is readily produced in a cyclotron and has a half-life of 5.5 days. Because of the low energy of the gamma radiation of xenon-133 there is a significant amount of scatter that mainly affects the white matter regions which have the lowest counting rate, making quantification of CBF difficult (Olesen, 1991).

During provoked attacks of migraine with aura, an oligoemia has been demonstrated to spread from the occipital lobe anteriorly across the cortex at a rate of 2-3mm/min, ultimately often involving the whole hemisphere and progressing without respect to the vascular territories. The latter suggests that the phenomenon is unlikely to be primarily vasoconstrictive in origin. In a small number of patients the attacks were initiated by focal hyperaemia (Lauritzen *et al.*, 1983; Olesen *et al.*, 1981). However the most consistent observation in numerous studies during spontaneous and provoked attacks of migraine with aura, in patients imaged during the aura phase, headache phase and after resolution of the headache, has been of focal cortical *hypoperfusion* during the aura phase, corresponding to the area from which the aura is assumed to originate. This may persist into the headache phase, and then is followed by a transitional period of normoperfusion and thereafter hyperperfusion in the same area. The hyperperfusion was seen to occur during the headache phase and persist into the headache-free phase before reverting to normal interictally. In almost all the individuals the focal changes in

cerebral blood flow were seen contralateral to the neurological symptoms; occasionally bilateral changes were observed with unilateral symptomatology or the converse. The side of the headache occurred most commonly on the side associated with the changes of regional cerebral blood flow (Andersen *et al.*, 1988; Friberg *et al.*, 1989; Friberg *et al.*, 1987; Lauritzen & Olesen, 1984; Olesen *et al.*, 1990; Olsen *et al.*, 1987). These observations confirmed the results of earlier xenon-133 cerebral blood flow studies in migraine with aura (O'Brien, 1971; Edmeads, 1977; Sakai & Meyer, 1978; Skinhoj, 1973; Staehelin-Jensen *et al.*, 1981). Persistence of abnormalities interictally in migraine with aura corresponding to the assumed origin of the aura symptoms in some patients has also been shown (Lagreze *et al.*, 1988; Lauritzen & Olesen, 1984; Schlake *et al.*, 1990). Sakai and Meyer showed impaired cerebral autoregulation up to 36 hours following the headache in patients with migraine with aura. Notably the interictal period was not detailed by Lagreze and colleagues (except that this was <6 days after the last migraine attack) who reported persistence of CBF abnormalities in patients with migraine with aura imaged interictally; Lauritzen and Olesen imaged all patients at least one week after the last migraine attack and made the same observation in only one patient of 11. Sakai and Meyer also showed an increase in mean extracerebral blood flow measurements during the migraine headache bilaterally but higher on the side of the headache attack (Sakai & Meyer, 1978).

5.1.3 Perfusion weighted magnetic resonance imaging in migraine with aura

The observations during migraine aura have been more recently confirmed with perfusion-weighted nuclear magnetic resonance imaging. Magnetic resonance imaging uses orthogonal magnetic and radiofrequency fields to provide anatomical information based on the proton relaxation properties and proton density of different tissues. The passage of a short bolus of a paramagnetic contrast agent such as gadolinium can be

followed through the brain by tracking changes in signal intensity obtained by a series of rapid images. The contrast agent remains intravascular as it cannot cross the blood-brain barrier. Gadolinium shortens both the T1 and T2 of the surrounding protons, resulting in a signal increase on T1 and decrease on T2-weighted images. This provides the required contrast for bolus tracking perfusion-weighted magnetic resonance imaging. From the concentration against time data information about relative cerebral blood flow can be obtained (Gadian, 1995). Four patients were imaged using this technique during episodes of spontaneous visual aura by Cutrer and colleagues (Cutrer *et al.*, 1998). A decrease in relative cerebral blood flow was observed in the occipital cortex contralateral to the side of the symptoms. Notably no change was observed in diffusion weighted images during aura and the interictal period suggesting that any alteration in cerebral blood flow does not reach ischaemic levels.

5.1.4. Xenon-133 and the use of stationary detectors and SPECT studies in migraine without aura

SPECT studies in patients with migraine without aura have been less consistent (Juge, 1988; Meyer *et al.*, 1986) but have suggested that regional cerebral blood flow is normal during the headache attacks and in between attacks (Ferrari *et al.*, 1995; Friberg *et al.*, 1989; Lagreze *et al.*, 1988; Lauritzen & Olesen, 1984; Sakai & Meyer, 1978).

5.1.5 Positron emission tomography (PET)

The annihilation event

PET uses a variety of radiotracers to visualise and quantitate different biochemical processes. The physical process behind PET is positron decay. When a positron, a particle of equal mass but opposite charge to an electron, is emitted as a result of the radioactive decay of an unstable radionuclide, it travels a distance of about 2-7mm before losing kinetic energy and combining with an electron, the so-called annihilation event. This event results in the creation of two photons of equal energy (511 keV) which travel in opposite directions close to 180°. The photons are detected by a cylindrical array of scintillation crystals (bismuth germinate or sodium iodide) which register a decay event when two photons enter crystals on opposite sides at the same time. The scintillation crystals fluoresce when struck by ionising radiation and are linked to photomultiplier tubes which convert the scintillations to electronic signals. Collection of about 0.5-1 million coincident events by the circumferential array of paired detectors is registered and reconstructed by computer to generate an image. Annihilation events outside of the detector are not registered. A coincidence event identifies a line upon which the annihilation occurred, ie a coincidence line. The large number of intersecting coincidence lines forms the basis for the PET image, and are stored as a function of distance from axial centre of the tomogram and angle offset with respect to the scanner axis as a two-dimensional matrix or sinogram. The PET image is reconstructed from the latter by the technique of filtered back projection (Wolf & Fowler, 1995). This method of data recording (sometimes referred to as electronic collimation) offers a number of advantages compared to conventional single photon detection techniques (in which lead collimators are used). It offers accurate methods for attenuation correction, uniform resolution and sensitivity.

Attenuation correction

When a gamma ray-emitting source is located within tissue, the count rate of photons with maximum energy recorded by an external detector will be less than when it is placed in air. This is due to absorption and scatter of the emitted photons by the intervening tissue. The first requirement for the performance of absolute measurements of tissue tracer concentrations is a means to correct for photon attenuation. This requirement is fulfilled by using coincidence detection because the lines along which the events have occurred are identified. An attenuation factor can be obtained from the thickness and attenuation coefficients of the body tissue. The chance that both photons emerge from the body and are recorded by opposite detectors is the same as that for one photon (with the same energy) travelling the same total pathlength through the tissue. Therefore the attenuation factor can be measured by placing a ring positron-emitting source in the plane from which the emission data is gathered (ie around the body). From this source one of the annihilation photons has to travel the total distance through the body while the second photon is not attenuated at all. Thus prior to gathering emission data a transmission scan is performed through the same transaxial slice as the corresponding emission scan. In addition a blank attenuation scan is performed; this is a transmission scan without patient and bed in the field of view of the detectors (ie no attenuation). The ratio of transmission over the blank attenuation counts then provides the (measured) attenuation factors. From this a tomographically reconstructed transmission scan measures attenuation at all angles in that plane. Sensitivity of coincidence detection is depth dependant. Although attenuation of different photons will differ, the total attenuation of an annihilation pair depends only on the total attenuation length traversed through the tissue.

Spatial Resolution

Spatial resolution is independent of depth. Due to the finite size of the detectors, the response function of a pair of coincidence detectors is a function of the relative position of the source between the detectors. The resolution is better in the centre between the detectors than close to one of them. In addition there are variations in spatial resolution due to the angle between the detector and source and possible penetration of the detector, yet with a subsequent registration in the adjacent detector. Increasing the distance between detectors reduces the difference in position (and angle) between centre and edge of an object with respect to the detectors. Thus width of the response function depends on the detector width and for cylindrical detectors the response function is Gaussian; the quoted image resolution for a scanner is quoted as the full width and the half maximum (FWHM). Due to the kinetic energy of an emitted positron it will travel a finite distance (different for different radionuclides; usually about 0.5 cm FWHM) through tissue before annihilation. Due to the residual kinetic energy at the time of annihilation, the angle between the two annihilation photons will be slightly different (0.5° FWHM) from 180° . The effect of this on spatial resolution of the scanner depends on the distance between the opposing detectors (Lammertsma & Frackowiak, 1985).

Random Events and Scatter

Random events occur when two photons coming from two unrelated positron annihilation events are detected within the coincidence resolving time. Random coincidences are a source of error as they give rise to misplacement of events. This can be reduced by using lead slit shields around the detectors to protect them from off-plane activity. Monitoring of the random coincidence rate is done by using a delayed coincidence window. This can then be subtracted from the total coincidence rate to obtain the true coincidence rate.

Another source of error occurs when coincidence detection of an annihilation pair of which one or both of the photons have been scattered. This leads to wrong positioning. Because the photons recorded originate from a true coincidence event, it cannot be corrected for by delayed circuitry. Therefore counts with a pulse height corresponding to a narrow window around 511 keV. However this greatly reduces the detection efficiency and could affect stability. Typically the window threshold is set at 100-150 keV because many low-energy events result from partial interactions of 511-keV photons in the detector itself. However the slit shielding mentioned greatly reduces the detection of off-plane scatter. When the detectors are far apart (1 meter) the detection efficiency of the remaining in-plane scatter is small because of the small solid angle for detection. Most of the scattered rays leave this small solid angle (Lammertsma & Frackowiak, 1985).

Positron Emitters

The four of the major positron emitters used to label organic molecules are carbon-11, fluorine-18, nitrogen-13 and oxygen-15. These can be substituted for corresponding stable elements in organic molecules to produce a radiotracer that retains the properties of the parent compound and whose participation in a definable biochemical process can be followed. Two of the main radiotracers for the brain are 2-deoxy-2-[^{18}F]fluoro-D-glucose which is used to measure glucose metabolism; and oxygen-15 labelled water which measures perfusion. Temporal resolution depends on the half-life of each positron emitter. The positron-emitting isotopes mentioned are short-lived which allows good temporal resolution and they can be readily generated in a cyclotron. The PET technique of a bolus injection of ^{15}O labelled water is used to measure perfusion as an index of synaptic activity. Because the half-life of this radioisotope is 123 seconds, the rapid decay of the radioisotope to background radioactivity allows rapid sequential

imaging at 8 minute intervals. Although both SPECT and PET detect radiotracer distribution, the chemical versatility of positron emitters is greater, their concentration can be measured quantitatively with relatively little attenuation by other tissues, and the spatial and temporal resolution is better.

5.1.6 PET in migraine with and without aura

The first PET study report was by Herold and colleagues who used a ^{15}O steady-state inhalation technique to measure cerebral blood flow (CBF), oxygen extraction ratio and cerebral oxygen consumption (Herold *et al.*, 1985). The small study confirmed the results of the earlier studies discussed above, that is, focal reductions in CBF during the early phase of migraine aura (contralateral and consistent with the site of origin of the aura symptoms), but no changes in the later phase of the attack nor during an attack of migraine without aura. Moreover, in contrast to previous reports suggesting that the observed reduction in cerebral blood flow may reach ischaemic levels (Olsen *et al.*, 1987; Skinhoj, 1973), there was normal metabolism, maintained by increased fractional oxygen extraction ratio despite the hypoperfusion. No changes in oxygen metabolism were observed in the later phase of migraine with aura nor during migraine without aura. There have been two more recent fully published PET studies in migraine. The first was reported in 1994 by Woods and colleagues (Woods *et al.*, 1994). A 21 year old woman gave a history of regular almost weekly attacks of migraine without aura. The woman happened to be in a PET scanner performing a visual stimulation task when she began to experience a throbbing headache accompanied by photophobia and nausea. During the attack she described some difficulty in focusing but no characteristic aura symptoms, however she did subsequently during the attack experience an episode of vertigo. Bilateral decreases in blood flow were observed in the visual association cortices during the 7th of 12 scans following onset of the headache. With each

subsequent scan thereafter a decrease in regional cerebral blood flow occurred across the cortical surface progressing anteriorly at a constant rate sparing the cerebellum, basal ganglia and thalamus. The study reports the case as one of migraine without aura. This would certainly be a landmark study in this instance. There has always been debate as to whether migraine with and without aura form two ends of a spectrum or whether they are truly distinct syndromes pathophysiologically. But there needs to be some caution about the diagnosis of migraine without aura in this individual in view of the symptoms of vertigo and the findings which are consistent in previous studies of migraine with aura but have never been shown in migraine without aura.

In 1995 Weiller and colleagues published a PET study of 9 patients with migraine without aura who were imaged within 6 hours of onset of an acute attack (Weiller *et al.*, 1995). The individuals were imaged during the same session following effective treatment with subcutaneous sumatriptan and then again at a different session when pain free in between attacks. Sumatriptan has been shown not to alter regional cerebral blood flow (Ferrari *et al.*, 1995; Friberg *et al.*, 1991; Scott *et al.*, 1992). The analysis showed activation during headache bilaterally in the cingulate cortex and in the inferior anterocaudal cingulate cortex on the left, which was attributed to the emotional response to pain; the auditory association cortices and the parieto-occipital junction in the visual association cortex, tentatively attributed to the phonophobia and photophobia, but also in the brain stem. The activation in the brainstem was slightly lateralised to the left and although the resolution of the PET study was not adequate enough to distinguish individual nuclei, the activation seen was considered to be in the region of the midbrain periaqueductal grey, dorsal raphe nucleus and the dorsolateral pontine tegmentum, including the locus coeruleus. This activation persisted after treatment into the pain free state whilst activations elsewhere diminished. One of the theories

regarding the pathogenesis of migraine is of a primary dysfunction of the trigeminal nociceptive and the midbrain antinociceptive systems (the latter including the periaqueductal grey and the dorsal raphe nucleus) and the autonomic control of cerebral and dural blood flow by the dorsal raphe nucleus and the locus coeruleus (Goadsby & Lance, 1988). The only direct evidence of pain generated from the brain stem at the time was based on a report by Raskin, and later supported by Veloso *et al.*, of non-headache patients who developed migraine-like headaches after stereotactic intervention by creation of a lesion in the region of the periaqueductal grey (Raskin *et al.*, 1987; Veloso *et al.*, 1998). Moreover these attacks responded to specific serotonergic agonists used in the treatment of migraine headache. Haas and colleagues have reported a case of a migraine-like headache in a patient with multiple sclerosis who presented with a single enhancing lesion in the region of the periaqueductal gray. With a course of corticosteroid therapy the symptoms and lesion on MRI resolved (Haas *et al.*, 1993). The persistence of the brain stem activation following resolution of the migraine attack was thus postulated to be responsible for development of the migraine attack rather than part of an antinociceptive response to the head pain.

5.2 Functional imaging studies in cluster headache

5.2.1 Xenon-133 with the use of stationary detectors and SPECT studies in cluster headache

In 1978 Sakai and Meyer imaged 7 patients with cluster headache during presumed spontaneous attacks of pain using inhaled Xenon-133 and the use of stationary detectors (Sakai & Meyer, 1978). Five patients were imaged when headache-free; three patients were imaged during the headache attack and when headache-free. Regional increases in cerebral blood flow were seen in the precentral, parietal and sylvian-opercular regions contralateral to the head pain and were thought to be secondary to the head pain. There

were also increases in the extracerebral circulation greater on the side of the head pain which was thought to be the primary cause of the pain. There have been few functional imaging studies in cluster headache. In 1984 Krabbe and colleagues imaged 18 patients with chronic cluster headache and episodic cluster headache during the active period with inhaled xenon-133 SPECT (Krabbe *et al.*, 1984). Alcohol 12g was used to attempt to trigger attacks of cluster headache. If this was not successful after an hour, nitroglycerine 1mg sublingually was given. One patient experienced a spontaneous attack. Eight patients developed attacks of cluster headache following provocation. Comparing the pain state to the pain free state significantly increased regional cerebral blood flow was seen in the right parietotemporal region and attributed to the response to pain. In the nine patients imaged following alcohol/nitroglycerine administration who did not develop a cluster headache attack no focal individual or group abnormalities in cerebral blood flow were observed. No significant changes of mean cerebral blood flow from baseline were seen in all the patients whether or not an acute cluster headache attack was experienced. Schlake and colleagues imaged 5 patients with cluster headache interictally with SPECT using ^{99m}Tc -D-L-hexa-methyl-propylen-amine-oxime (^{99m}Tc -HMPAO) (Schlake *et al.*, 1990). This is a lipophilic tracer which crosses the blood brain barrier. It is distributed in proportion to regional cerebral blood flow trapped in the brain by its conversion from a lipophilic to hydrophilic form. Although the spatial resolution of ^{99m}Tc -HMPAO is better than with the xenon-133 method, the retention of the tracer in the brain limits the temporal resolution which is essential during acute attack studies. However the technique can be used interictally. In this study the uptake of the tracer was normal or non-specifically altered in all the patients with cluster headache.

Based upon the hypothesis that cluster headache may be caused by an inflammatory

process in the region of the cavernous sinus as discussed in Chapter 3, Gawel and colleagues imaged six patients interictally but during the active bout with gallium SPECT (Gawel *et al.*, 1990). Three patients were found to have an area of increased activity in the parasellar region in close relation to the cavernous sinus which faded as the patients moved out of their active cluster period. Computerised tomography had been normal in three patients. Subsequently Sianard-Gainko and colleagues imaged 30 patients with cluster headache and 7 with migraine without aura with gallium SPECT (Sianard-Gainko *et al.*, 1994). Parasellar hyperactivity was judged as present in 81% of chronic cluster headache patients, 54% of episodic cluster headache patients in the active period, 56% of episodic cluster headache patients in remission and 71% of migraineurs. No significant correlations were found between the SPECT images and the duration of the disease, of cluster periods or of remissions. It was therefore postulated that increased parasellar activity on Gallium SPECT was not specific for cluster headache, nor for the active period of cluster headache. Afra and colleagues imaged 15 patients with ECH with ^{99m}Tc -HMPAO SPECT. In 7 imaged in and out of a GTN induced cluster headache attack there was no difference in rCBF between the two conditions. In 2 cases there was moderate hypoperfusion of both frontal lobes and in 6 frontal bilateral hyperperfusion during the attack. Using transcranial Doppler, blood flow velocities in the middle cerebral artery ipsilateral to the side of the headache were significantly decreased during the headache attack compared to the headache-free state (Afra *et al.*, 1995). More recently Di Piero and colleagues imaged 7 episodic cluster headache patients in remission and 12 volunteers with xenon-133 SPECT using the cold water pressor test as an experimental model of tonic pain stimulation (Di Piero *et al.*, 1997). During the cold water pressor test, volunteers showed a significant cerebral blood flow increase in the contralateral primary sensorimotor, frontal and temporal cortices and thalamus, and, in the ipsilateral temporal and anterior cingulate regions.

During left-hand stimulation (ipsilateral to the headache side) by cold water pressor test in cluster headache patients, cerebral blood flow changes were significantly lower than those observed in volunteers in the contralateral primary sensorimotor region and thalamus region. There were no significant differences in the brain response observed during the stimulation of the hand contralateral to the headache side, suggesting modification of central pain processing in patients with cluster headache.

5.2.2 PET studies in cluster headache

Prior to the work detailed in this thesis, there had been a single PET study in patients with cluster headache. [¹⁵O]Butanol was used as a tracer for cerebral blood flow. Sublingual nitroglycerine was successful at triggering an acute attack of cluster headache in four of seven patients with episodic cluster headache in the active bout. Two had right and two left sided attacks. A total of six scans were performed, two at baseline, one following nitroglycerine, two during headache and one following the administration of 6mg subcutaneous sumatriptan. The regions seen to be activated in the pain state compared to the pain free state were the anterior cingulate cortex and the right temporal cortex. Activation of these areas has been attributed to the processing of pain and in particular is supportive of right hemispheric specialisation in the mediation of withdrawal related negative affect (Hsieh *et al.*, 1996a). Notably the number of patients imaged was small.

5.3 Summary

Since the time of Wolff's original observations, the concept of migraine and cluster headache as 'vascular headaches' has come under much scrutiny. The hypothesis that the aura phase of migraine is caused by vasoconstriction and the headache from vasodilatation is too simplistic and not supported by the observations of the reviewed

functional imaging studies. These suggest the primary phenomenon to be neurally driven. Clinical and experimental observations of cluster headache suggest central mechanisms to be fundamental to the pathophysiology of the syndrome. Functional imaging studies in cluster headache however have been few. These have been hampered by small patient samples and different, often limited, techniques. The most consistent finding during the acute attacks has been activation of structures associated with the response to, and processing of, painful stimuli. The more recent techniques using H_2O^{15} -labelled PET provide adequate spatial and temporal resolution to further address central mechanisms in cluster headache.

PART 2

PET STUDIES OF CLUSTER HEADACHE

Chapter 6

Oxygen-15 Tracer Positron Emission Tomography

6.1 Introduction

The basic principle behind positron emission tomography has been detailed in Chapter 5. The studies presented in this thesis have used PET to measure relative regional cerebral blood flow (rCBF). The use of this technique is predicated on the fact that increases and decreases of synaptic activity in the brain are accompanied by appropriate and equivalent changes in local glucose consumption and perfusion (Frackowiak & Friston, 1994). The method is well established (Frackowiak *et al.*, 1997; Raichle, 1981). The model upon which the search for regionally specific effects is based is that of functional segregation. The functional role played by any component (e.g. a neuron) of a connected system (e.g. the brain) is largely defined by its connections. Functional segregation demands that cells with common functional properties are grouped together; this in turn necessitates both convergence and divergence of cortical connections. Extrinsic connections between cortical regions are not continuous but occur in clusters. This clustering does in instances have a clear relationship to functional segregation. For example, V2 has a distinctive cytochrome oxidase architecture, consisting of thick, thin and inter-stripes. When recordings are made in V2, directionally selective, but not wavelength or colour selective, cells are found exclusively in the thick stripes. Retrograde labelling of cells in V5 is limited to these thick stripes. All available physiological evidence suggests that V5 is a functionally homogenous area specialised for visual motion. If it is the case that neurons in a given cortical area share a common responsiveness, by virtue of their extrinsic connectivity, to some sensorimotor or cognitive attribute, then this functional segregation is also an anatomical one. Challenging the subject to the appropriate attribute should thence lead

to activity changes in the area of interest only, which has been confirmed (Mintun *et al.*, 1989).

6.2 Method

Regional cerebral blood flow in the studies detailed in this thesis was measured using the positron emitting isotope oxygen 15 to label water (H_2O^{15}). The tracer has a half-life of 2.1 minutes. PET measures changes in blood flow or perfusion directly in terms of amount of radiolabelled water that accumulates locally; however this takes several tens of seconds up to a minute. By virtue of the half-life of the tracers used, PET can only measure responses summed over fairly long periods of time. Consequently PET can only be used to measure differences between brain states.

Camera characteristics

Coincidence detection for positron imaging in clinical studies was first suggested in 1951 using single probes in coincidence. Later a positron imaging device using a scintillation camera was described, However these systems were used for two-dimensional imaging. Transverse section imaging with positrons was first described in 1962 using a circular array of sodium iodide detectors, followed by a rotating multicrystal positron camera. The first major advance was in 1974 when the first positron emission tomograph using a Fourier-based reconstruction algorithm, proper sampling and exact attenuation correction was described. In this design, noise (scatter and random events) was minimised by placing the detectors around a single transaxial slice and shielding them from off-plane activity using lead slit shields. The final version, the PETT-III (Positron Emission Transaxial Tomography) was the first whole-body tomograph specifically designed for human studies. From this came the first commercial tomograph, the ECAT (Emission Computerised Axial Tomograph). This

was subsequently modified to correct for random coincidences using delayed circuitry (Lammertsma & Frackowiak, 1985). Performance characteristics were improved by introducing the capability of data acquisition in both 'conventional' two-dimensional mode (with septa) and three-dimensional mode (septa retracted); in spite of increase in scatter when the septa are retracted, the increased efficiency in the three-dimensional mode of acquisition yields distinct advantages, particularly in studies where tracer concentration is low and random rates less important (Spinks *et al.*, 1992). Spinks and colleagues described the basic detector unit of the tomograph to be a block of Bismuth germinate crystals cut into 64 elements (8 x 8) and viewed by four square photomultipliers in two dual envelopes. The scanner described consisted of two rings of block detectors, thus 16 rings each. Fifteen inter-ring septa consisted of parallel-sided tungsten annuli. Extension and retraction of septa was accomplished by software control. In the two-dimensional mode transaxial images were formed by filtered back projection normally into a matrix of 128 x 128 pixels (giving a pixel size of 2 x 2 mm). With septa retracted all 256 (16 x 16) inter-ring coincidences can be acquired (three-dimensional). The 256 sinograms are stored separately for reconstruction using a fully three-dimensional algorithm. In this the spatial invariance of the axial point response function is achieved by forward projecting the conventional two-dimensional image planes to provide the unmeasured projections. A three-dimensional image is then formed by backprojecting the original and forward-projected sinograms and applying a three-dimensional filter. The three-dimensional image volume comprises 128 x 128 (transaxial, x, y) x 31 (axial, z) voxels; the latter dimension is arbitrary (the 31 corresponds to 31 two-dimensional planes each of slice spacing 3.4mm in the z direction).

Commercial scanners consists of multiple detector rings to scan a number of transaxial planes simultaneously. The PET scans in this thesis were obtained with an ECAT scanning system (ECAT EXACT HR+, CTI Siemens, Knoxville, Tennessee, United States of America) in three-dimensional mode with collimating septa retracted. The intensity of the PET image is a function of the density of the photon annihilation events at that point. To calibrate the camera a container of uniform construction containing a uniform quantity of radionuclide is imaged and radionuclide activity measured in a calibrated well counter against which the PET image may be scaled to represent absolute radioactivity. The corrected data were reconstructed into 63 transverse planes (separation 2.4 mm) and into a 128 x 128 pixel image matrix (pixel size 2.1 mm) by three-dimensional filtered back projection. After reconstruction the dynamic images from each scan were transferred to a Sun SPARC workstation on which all calculations and image transformations were performed. The data were analysed by Statistical Parametric Mapping software (SPM '99 <http://www.fil.ion.ucl.ac.uk>, Welcome Department of Imaging Neuroscience) implemented in MATLAB (Mathworks INC., USA).

Method

The subjects' head was placed in the tomogram in a supportive moulding. Line markings were drawn on the subjects' orbito-meatal lines and centrally on the forehead. Correct position in the scanner, perpendicular to a line approximately between the anterior and posterior clinoids, was maintained by alignment of these markings with perpendicular laser lines on the camera gantry. A 5 minute transmission scan was obtained to ensure correct positioning of the subject within the camera's field of view, allowing head adjustment if required followed by a further short transmission scan. This was followed by a 20 minute transmission scan obtained prior to collection of the

emission data to correct for radiation attenuation by tissues in the head. For each measurement of rCBF 9 milliCuries of H_2O^{15} was given as an intravenous bolus over 20 seconds followed by a 20 second saline flush. Integrated radioactivity counts were accumulated over a 90 second acquisition period, beginning 5 seconds before the peak radioactivity registered in the head. This allows up to 13 consecutive scans to be obtained at a minimum of 8 minute intervals, which allows adequate time for decay of the radioactivity.

6.3 Statistical Analysis

The details of the following statistical analysis are comprehensively discussed in: Frackowiak, R.S.J., Friston, K.J., Frith, C.D. & Mazziotta, J.C. (1997) *Human Brain Function*, First edn. Academic Press, London.

Coregistration

Most single patient studies require about 90 minutes for acquisition of the 12 - 13 scans and the relevant conditions of interest. Movement of head position is therefore inevitable. Moreover some patients had to come out of the scanner between conditions of interest. Thus despite repositioning using the facial line markings head position will not be identical during each PET scan. The first step of the analysis addresses movement-related variance. Each image is coregistered with reference to the first to correct for motion artefact.

Normalisation

To implement voxel-based analysis of imaging data, data from different subjects must derive from homologous parts of the brain. Spatial transformations are therefore applied that move and 'warp' the images such that they approximately conform to a standard

brain. This normalisation facilitates intersubject averaging and the reporting of results in a conventional way. The transformation of an image into a standard stereotactic anatomical space corresponds to spatial normalisation. The data is usually spatially normalised into the standard stereotactic space defined by the atlas of Talaraich and Tournoux, a template created at the Montreal Neurological Institute, from an average of 305 normal structural magnetic resonance scans.

Smoothing

Smoothing (convoluting the data with a smoothing kernel) has a number of objectives. First it increases the signal to noise ratio. The neurophysiological effects of interest are produced by haemodynamic changes that are expressed over spatial scales of several millimetres, whereas noise usually has higher frequencies. For PET the spatial frequency structure of noise is determined by the reconstruction process used to create the images. Secondly, convolving with a Gaussian kernel conditions the data to conform more closely to a Gaussian field model. Thus the theory of Gaussian fields can be used to make statistical inferences, ie assign p-values to the observed regional specific effects. The final reason for smoothing is specific to intersubject averaging. It ensures that haemodynamic changes from subject to subject are assessed on a spatial scale at which homologies in functional anatomy are typically expressed, e.g at a scale of a hundred microns to a millimetre, it is unlikely even with perfect spatial normalisation that the functional anatomy and organisation of the frontal gyri in two subjects will show meaningful homologies. However at an anatomical scale of e.g 8mm they do, as shown by the success of multi-subject PET activation studies. The presented normalised images in this study were smoothed with a Gaussian filter of 10mm full width half maximum.

Global changes in cerebral blood flow

Global cerebral blood flow varies both between subjects and over time in a single individual. If qualitative “count” measurements of relative activity are being used as an indicator of rCBF, then changes in the global activity reflect changes in the administered dose and head fraction, as well as changes in global cerebral blood flow. Therefore, changes in rCBF (or relative activity) measurements across experimental conditions, (measured at different times and on different subjects), are confounded by global changes. For normal subjects the global CBF is adequately measured as the mean rCBF over all intracerebral voxels. The contribution of global CBF to the variance in rCBF is removed by a voxel-by-voxel analysis of covariance (ANCOVA) with global CBF as the confounding variable. For each voxel a regression line is calculated describing the relationship between regional and global flow for each subject across the study conditions. A voxel-by-voxel map can thence be generated resulting in condition-specific adjusted rCBF values, normalised to a global activity of 50 ml blood / 100 mg brain / minute, with an associated adjusted error variance. Implicit in allowing for changes in global CBF when assessing condition specific changes in rCBF, is the assumption that global CBF represents the underlying background flow, above which regional differences are assessed ie global CBF is independent of condition. There have been few studies which have addressed the effect of pain on global CBF and the results are conflicting (Coghill *et al.*, 1998; Sakai & Meyer, 1978; Sakiyama *et al.*, 1998). Thus all results presented in the following studies are adjusted for effects of global CBF.

Regional changes in cerebral blood flow and Statistical Parametric Mapping (SPM)

In SPM each voxel of the brain is analysed using a univariate statistical test. The resulting statistical parameters are assembled into an image - the SPM (statistical

parametric map). SPMs are interpreted as a spatially extended statistical process by referring to the probabilistic behaviour of stationary Gaussian fields. Excursions of the SPM are interpreted as regionally specific effects, attributable to a sensorimotor or cognitive process. The experimental design and model used to test for specific neurophysiological responses are embodied in a mathematical structure called the design matrix. Statistical parametric mapping partitions the design matrix according to whether the effect is of interest (ie an activation) or not (e.g a nuisance effect like global activity). The contribution of each effect, ie each column of the design matrix modelling the various response components to the observed physiological responses, is estimated using the general linear model and standard least squares. These estimated contributions are known as parameter estimates. Regionally specific effects are framed in terms of differences among these parameter estimates (e.g an activation effect) and are specified using contrasts. The significance of each contrast is assessed with a statistic that has Student's t-distribution under the null hypothesis. For each contrast, or difference in parameter estimates, a statistic is computed for each voxel in the brain to form an SPM $\{t\}$. For convenience the SPM $\{t\}$ is transformed to a Gaussian Field or SPM $\{Z\}$. Statistical inferences are then made about local excursions of the SPM $\{Z\}$ above a specified threshold, using distributional approximations from the theory of Gaussian fields. These distributions pertain to the maximal value and spatial extent of the observed activations. The resulting p-values can be corrected for the volume of the brain tested. However in the studies presented in this thesis an uncorrected threshold of $p < 0.001$ was chosen because of a strong regional *a priori* hypotheses based upon the clinical, experimental and functional imaging data cited in the introductory chapters.

6.4 Ethics Approval

The studies were approved by the Ethics Committee of the National Hospital for Neurology and Neurosurgery and permission to administer radioactive substances was obtained from the Advisory Committee on Radioactive Substances, U.K.

Patients were recruited from clinics at the National Hospital for Neurology and Neurosurgery. Affected individuals were recruited through quarterly support group newsletters (the Migraine Trust and Migraine Action Association) and direct mailing. Only patients diagnosed with headache according to the criteria of the Headache Classification Committee of the International Headache Society (Headache Classification Committee of the International Headache Society, 1988) were included in the studies.

CHAPTER 7

PET Study 1 - Acute Cluster Headache Attacks

7.1 Introduction

The clinical syndrome of cluster headache is characterised by unilateral first division trigeminal head pain and ipsilateral autonomic features. However, distinctive to the syndrome is the circadian and circannual rhythmicity of the symptoms. This is supported by abnormalities of hypothalamic determined functions as detailed in chapter 3 - Pathophysiology of Cluster Headache. However, cluster headache has been considered a 'vascular headache' for many years; this stems from the work done in the early part of the twentieth century which identified the principal pain-producing structures in the head to include the blood vessels (Feindel *et al.*, 1960; Penfield & McNaughton, 1940; Wolff, 1963). To provide a more complete explanation of the symptoms an integrated neurovascular hypothesis has been proposed (Goadsby *et al.*, 1991). PET was used primarily to address the role of central mechanisms in the pathophysiology of cluster headache.

Short attack duration and availability of the appropriate investigative facilities confound investigating spontaneous attacks of cluster headache. Triggering attacks can circumvent this problem. GTN triggered attacks of cluster headache have been shown to be clinically (Ekbom, 1968) and experimentally (Fanciullacci *et al.*, 1997) identical to spontaneous attacks (Goadsby & Edvinsson, 1994a). Moreover, both GTN (Dahl *et al.*, 1989; Hsieh *et al.*, 1996a; Krabbe *et al.*, 1984) and sumatriptan (Scott *et al.*, 1992) have been shown not to significantly alter regional cerebral blood flow.

7.2 Methods

Nine right-handed men (aged 25-67 years, mean 43 years) and one woman (54 years) with chronic cluster headache were studied during an induced attack of cluster headache. The attack was provoked by administration of 1.2mg sublingual GTN. All patients studied were not on prophylactic treatment for cluster headache and were otherwise healthy. All patients had had a normal structural T1-weighted MRI scan during the study.

Study Design

During the active study period each of the nine study patients had 12 or 13 consecutive scans in four conditions: baseline, after application of GTN, following the onset of an acute cluster headache attack, and once headache-free following successful treatment with 6mg subcutaneous sumatriptan. For each scan, patients rated their headache intensity with a visual analogue score (0 = no pain, 10 = the most severe pain). Participants had their eyes closed throughout the study.

Data analysis

Statistical parametric maps were derived with pre-specified contrasts to compare rCBF during headache versus rCBF after GTN administration and compared to the headache-free conditions. Since cluster headache is a strictly lateralised syndrome, the PET images were mirrored in the axial plane in patients with right-sided headache.

7.3 Results

Cortical and Subcortical activations

All patients developed a cluster headache attack following GTN; the one female patient developed a spontaneous cluster headache attack and will be discussed separately. Of

those with triggered attacks, five patients suffered a left-sided attack and four right-sided. All attacks were consistent with IHS classification criteria for cluster headache and described to be similar to the patients' spontaneous attacks. Details of scans and conditions for each patient are shown in Table 7.1. Comparing the condition of headache to headache-free state significant activations were observed in the ipsilateral hypothalamic grey area, bilaterally in the anterior cingulate cortex, in the contralateral thalamus, the ipsilateral basal ganglia, bilaterally in the insulae and in the cerebellar hemispheres (Table 7.2). Figure 7.1a shows significant activation detected adjacent to the third ventricle, slightly lateralised to the left and rostral to the aqueduct. The activation is ipsilateral to the pain side, lies in the diencephalon and coincides in the Talairach atlas with the hypothalamic grey matter. Figure 7.1b shows significant activation detected in the insular and frontal cortices, and in the hypothalamic grey matter. The activation in the hypothalamic grey area was seen only during headache with no significant activation seen following treatment of the attack with sumatriptan compared to the baseline condition.

Extracranial activations

There was significant activation outside the brain in regions corresponding to the intracranial vessels when comparing the post-GTN condition (before development of the acute cluster headache attack) with rest. This activation persisted and significantly increased during the acute headache attack with subsequent resolution into the pain-free state following successful treatment of the attack (Figure 7.2 and 7.3).

Spontaneous cluster headache

One patient had a spontaneous right-sided cluster headache attack whilst in the PET scanner. Significantly this patient demonstrated the same extracranial changes during

the acute headache attack as the patients with GTN-triggered attacks (Figure 7.5). Subcortical and cortical activations did not reach significance.

7.4 Discussion

Areas of activation were observed during acute cluster headache which fall into three groups: areas known to be involved in pain processing or the response to pain, such as the cingulate and insula cortices and thalamus (Derbyshire & Jones, 1998); areas activated specifically in cluster headache but not in other causes of head pain, ie the region of the posterior hypothalamic grey; and activation of the cranial vessels. These data suggest that primary headache syndromes share some processing pathways but equally can be distinguished on a functional neuroanatomical basis by areas of activation specific to the clinical presentation.

Pain processing areas

Studies with PET have repeatedly given results that show activation of the anterior cingulate cortex (ACC, BA 24) on the sensation of somatic or visceral pain that are attributed to the emotional response to pain (Hsieh *et al.*, 1996a, Casey *et al.*, 1994; Rosen *et al.*, 1994). Activations in the insula have been shown after application of heat (Casey *et al.*, 1994; Minoshima *et al.*, 1995), subcutaneous injections of alcohol (Hsieh *et al.*, 1996b), somatosensory stimulation (Burton *et al.*, 1993) and during cluster headache (Hsieh *et al.*, 1996a). Given its anatomical connections, the insula has been suggested as a relay of sensory information into the limbic system and is known to play an important part in the regulation of autonomic responses. Painful stimuli are effective in activating the anterior and posterior insula which are closely associated with both the somatosensory and limbic systems. Such connections may provide one route through which nociceptive input is integrated with memory to allow the full appreciation of the

meanings and dangers of painful stimuli. In the acute pain state the thalamus is a site where activations would most be expected. Activation of the contralateral thalamus as a result of pain is known from studies on animals (Goadsby *et al.*, 1991) and functional imaging studies in human beings (Derbyshire & Jones, 1998). Second to the ACC, activation of the insula and thalamus are the most consistent responses to pain observed with functional imaging (Derbyshire & Jones, 1998). The responses of the prefrontal cortex (BA9/10), closely interrelated with the ACC, have been attributed to the behavioural and attentional system involved in anticipation and planning a course of action during pain (Derbyshire *et al.*, 1997; Hsieh *et al.*, 1995). The role of the basal ganglia during pain is uncertain. The connections of the basal ganglia to the thalamus and thence the prefrontal cortex, the premotor cortex, supplementary motor area (BA6), the motor cortex and the ACC provide the essential circuitry associated with preparation to move (Derbyshire *et al.*, 1997; Iadarola *et al.*, 1998). While in the PET scanner patients are asked to try not to move. The cluster attack however is characterised by restlessness which may account for the observed basal ganglia activation. Activation of the cerebellar hemispheres during pain is not thought to be involved in the conscious perception of pain but involved in the integrated sensory-motor network (Ekerkot *et al.*, 1991; Iadarola *et al.*, 1998) and has been reported in previous PET studies of pain (Casey *et al.*, 1994; Hsieh *et al.*, 1995).

Areas specific to cluster headache

In contrast to migraine, no brainstem activation was observed during any of the analyses. A PET study of experimental head pain, induced by capsaicin injected into the forehead, has shown neither hypothalamic nor brainstem activation (May *et al.*, 1998b). Injection into the forehead activates the first division trigeminal afferents, the same fibres responsible for the pain activation in cluster headache. Thus two types of

first division trigeminal nerve pain, whilst sharing neuroanatomical pathways with cluster headache, do not give rise to hypothalamic activation. The finding implies that the activation is involved in the pain process in a permissive or triggering manner rather than simply as a response to first division trigeminal pain *per se*.

Hypothalamic activation in traumatic nociception has been observed in the region of the hypothalamus however the co-ordinates in this study correspond to a more posterior region of the hypothalamus than reported in the study by Hsieh and colleagues (Hsieh *et al.*, 1996b). The circadian and circannual rhythmicity of the symptoms of cluster headache (peak and trough frequencies of cluster period onsets in relation to photoperiod cues, nocturnal attacks coinciding with REM sleep, day-time clock-like regularity of attacks), cluster-period-bound alterations in hypothalamic determined neuroendocrine functions, and autonomic dysfunction (primarily parasympathetic), point towards dysfunction of the cells of the anterior hypothalamus. Other hypothalamic functions - drinking (lateral nucleus), eating (lateral and ventromedial nucleus), rage and fear (lateral and ventromedial nucleus) and memory (mamillary nucleus) are not typically disturbed, although there are no studies which have formally addressed these characteristics. Activations observed with perfusion PET studies indicate activation of the observed region of the brain as defined by the predetermined contrasts; however the limitation thence arises that the functional consequence of the activation cannot be determined from the imaging alone. The region of the hypothalamus activated in this study is posterior. The clinical syndrome suggests dysfunction of the anterior hypothalamus. Therefore it is plausible that the activation of the posterior hypothalamus has a modulatory influence on the anterior hypothalamus which results in dysfunction of the latter.

Extracranial areas

In keeping with the 'vascular hypothesis' cluster headache has been attributed to an inflammatory process in the cavernous sinus; the arguments for and against this hypothesis have been discussed in Chapter 3 - Pathophysiology of Cluster Headache. This study found increased signal in the region of the cavernous sinus in patients with acute cluster headache. However the same finding was observed in the PET study of experimental first division trigeminal pain induced by capsaicin injected into the forehead (May *et al.*, 1998b). Therefore activation was seen in the region of the cranial blood vessels in both primary *and* secondary first division trigeminal pain, suggesting that the involvement of the cranial vasculature is not an event which initiates the pain but an epiphenomenon of activation of the first division trigeminal fibres subserving nociception. Furthermore the same regions of activation were observed in the single spontaneous cluster headache attack, supporting the changes observed to be integral to the activation of first division trigeminal pain fibres, rather than to the effects of GTN.

Notably the temporal resolution of PET does not allow determination of the time of onset of the activation of the hypothalamus, structures associated with pain processing and vascular structures in relation to each other and to the cluster headache attack. The only conclusion which can be made is that the activations were observed during the cluster headache with resolution of the activations with resolution of the cluster headache. Sumatriptan rendered the patients headache free and diminished the activations in the parenchymal and extraparenchymal areas adjacent to the large vessels. It is not possible to distinguish whether this is due to the vasoconstrictive effect of sumatriptan or to a direct effect on the neural systems involved. Notably, inhibition of both trigeminal and vascular activation is observed in experimental animals following administration of Zolmitriptan (Goadsby & Edvinsson, 1994b).

7.5 Summary

This study therefore supports that cluster headache, far from being a primarily vascular disorder, is a condition the genesis of which is to be found in the central nervous system, more specifically in the region of the posterior hypothalamus.

Table 7.1**Number of Scans for each Condition of Interest**

Patient	Baseline	Post - Nitroglycerine	Cluster Headache	Post- sumatriptan	Side
1	1-3	4-5	6-9	10-12	Left
2	1-3	4	5-9	10-12	right
3	1-3	4	5-10	11-13	Left
4	1-3	4-6	7-10	11-13	Left
5	1-3	4	5-10	11-13	Left
6	1-3	4-6	7-11	12-13	right
7	1-3	4-6	7-10	11-13	right
8	1-3	4	5-8	9-12	Left
9	1-3	4	5-11	12-13	right

Table 7.2**Increases in blood flow during an induced attack of acute cluster headache compared to the pain-free state**

The activation is tabulated in terms of the activated brain regions and their Brodmann areas and the x, y and z coordinates to the standardised anatomical space and refer to the line joining the anterior and posterior commissures which is situated at 0mm. Each location is the peak within a cluster (defined as the voxel with the highest Z-score) $p < 0.001$ for all regions

Activated Brain Region	Brodmann Area	Talairach	Co-ordinates	(mm)	Z Score of Peak Activation
		x	y	z	
Left hypothalamus		-2	-18	-8	3.68
Right thalamus		6	-12	6	5.01
Right cingulate cortex	24	2	22	24	4.9
Right frontal lobe	10	26	54	-6	4.06
Right motor area (face)	6/44	-40	-2	32	3.29
Right insula	13	32	10	2	4.28
Left insula	13	-40	12	-8	4.37
Left basal ganglia		-20	-12	2	4.22
Cerebellum (vermis)		-2	-38	-10	3.09

Comparison of the nitroglycerine induced acute cluster headache attack and rest (no pain) conditions in nine patients with chronic cluster headache

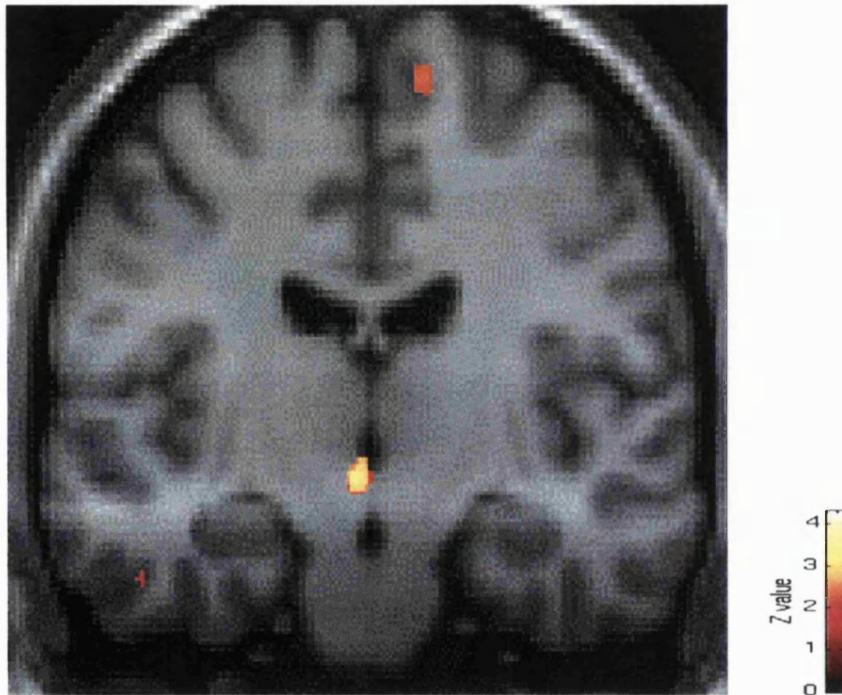


Figure 7.1a

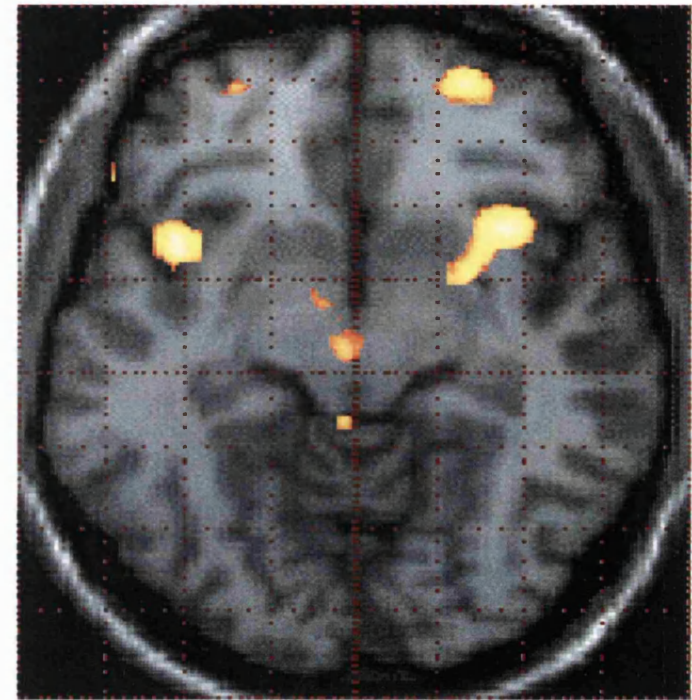
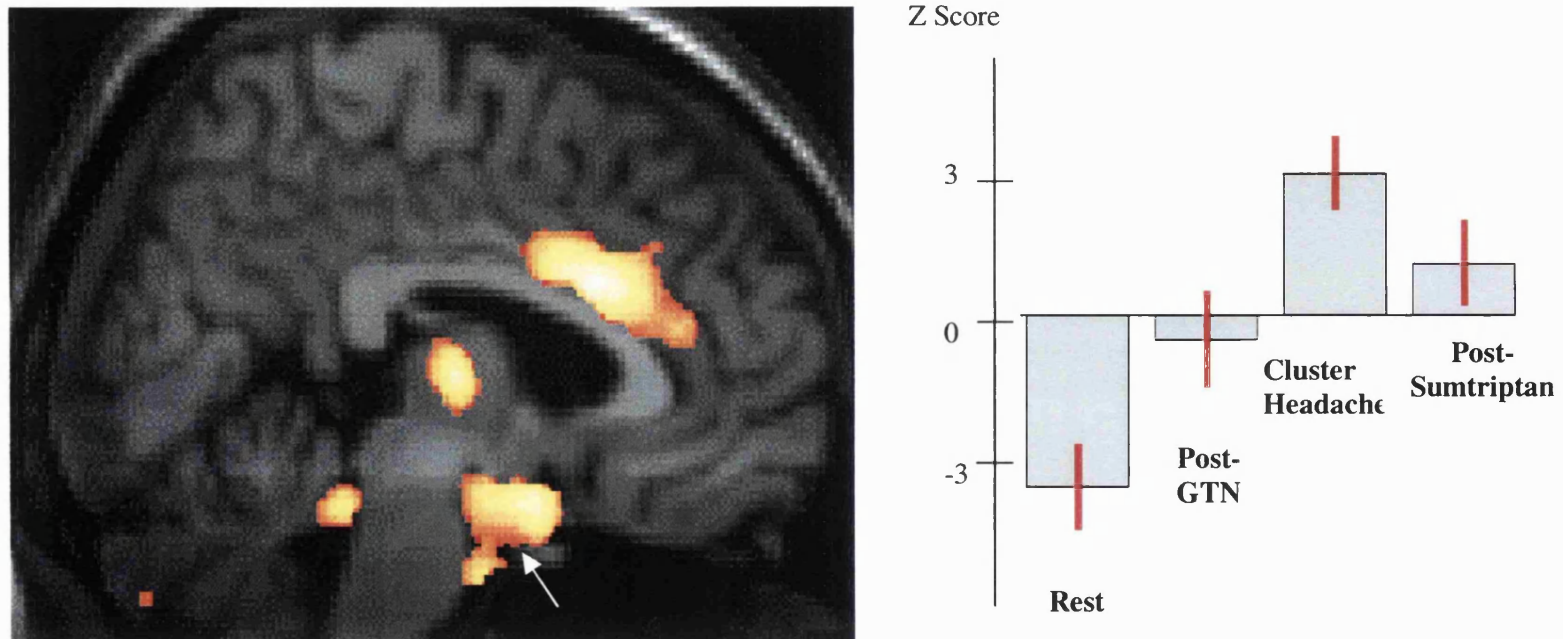


Figure 7.1b

Activations during the attack are shown as statistical parametric maps that show areas of significant rCBF increases ($p < 0.001$) in colour superimposed on an anatomical reference derived from a T1-weighted MRI. The left side of the picture is the left side of the brain.

Figure 7.2

Activation of structures involved in pain processing and of the intracranial vessels



Activation of the cingulate cortex, thalamus, cerebellar vermis and intracranial vessels (arrowed). The histogram shows the activation pattern in the region of the intracranial vessels in the four conditions of interest. The activation is shown as an excursion from the mean cerebral blood flow value given in terms of Z Score. The red line indicates the 95% confidence intervals.

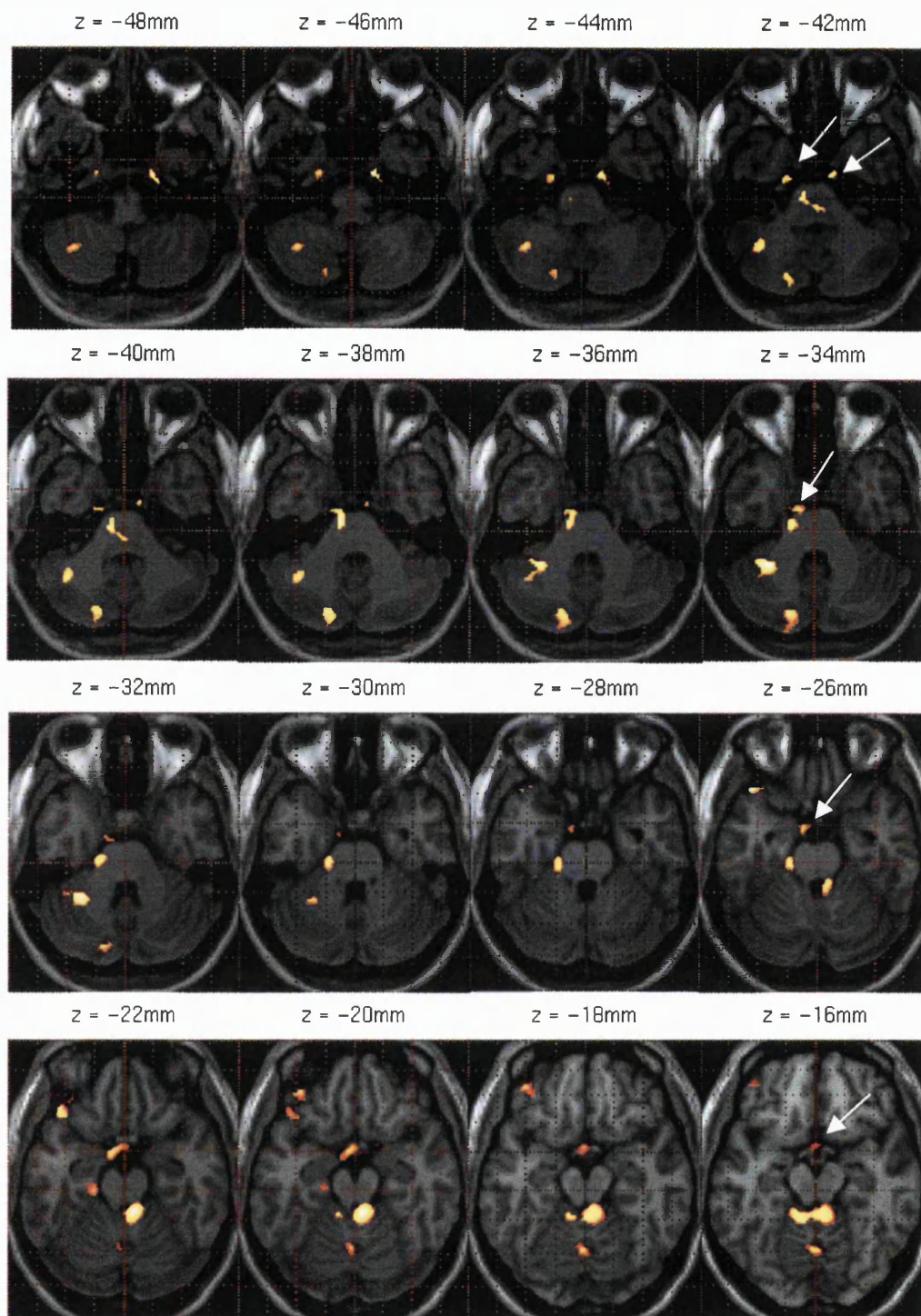


Figure 7.3

Comparison of GTN-induced acute cluster headache attack versus rest in nine patients with chronic cluster headache – Activation of the intracranial vessels

Significant activations were detected in intracranial vessels (arrowed) from -40 to -16 mm with respect to the anterior-posterior commissure line.

Figure 7.4



Activation of the Intracranial Vessels (arrowed) in a single case of spontaneous Cluster Headache

CHAPTER 8

PET Study 2 - Cluster Headache : A Comparison of Patients in and out of the Active Bout

Introduction

Cluster headache attacks can be triggered with GTN during the active bout without adverse effect. However during remission GTN is ineffective (Ekbom, 1968). In the context of attempted GTN attack induction, this second study sought to compare activations in the brain in patients during and out of the active bout using PET.

8.2 Methods

Eight patients with episodic cluster headache (31-61 years, mean 49 years; 6 men and 2 women) were studied out of the active bout. None were on prophylactic medication and all patients were otherwise healthy.

Study Design

The same study design as for PET Study 1 was followed.

Data analysis

The data were analysed for all patients out of the active bout separately, and with the active group (active cluster headache - CHA) detailed in PET Study 1 using a group-by-condition interaction analysis.

8.3 Results

None of the patients out of the active bout (inactive cluster headache - CHI) experienced an acute cluster headache attack following the administration of sublingual GTN. All experienced a mild generalised featureless headache (HA*) immediately following GTN which resolved spontaneously and was short-lived. Therefore the scans were defined for the conditions: Rest/CHI, HA*/CHI, No-CH/CHI and Rest Post-GTN/CHI to correspond with the timings of the scans in the active group (Rest/CHA, Post-GTN/CHA, Cluster Headache, Post-Sumatriptan - see Table 8.1) . Three scans were obtained in each condition. As cluster headache is a strictly lateralised syndrome, the PET images of patients (CHI) who usually experienced right-sided attacks, when in the active bout, were mirrored in the axial plane.

Table 8.1

Conditions of interest following GTN in patients with cluster headache in (CHA) and out (CHI) of the active bout

Patient Group	Condition 1	Condition 2	Condition 3	Condition 4
CHA	Rest	Post-GTN	CH	Post-Sumatriptan
CHI	Rest	HA*	No-CH	Rest Post-GTN

- CHA - active cluster headache
- CHI - Inactive cluster headache
- CH - Cluster headache
- GTN - Nitroglycerine
- HA* - Generalised mild featureless headache post-nitroglycerine

Cortical and subcortical activations (CHI)

Comparing the headache immediately after GTN (HA*) to rest, significant activations were observed bilaterally in the cingulate cortex (BA 24/32), right posterior thalamus, left basal ganglia, both frontal lobes (BA10), bilaterally in the insulae, and the left temporal lobe (BA 42) (see Table 8.2). These activations had resolved on comparison of the Rest Post-GTN and Rest conditions.

Extracranial Activations (CHI)

Comparing the headache immediately after GTN (HA*) to rest, there was significant activation in the region of the large intracranial vessels. This activation diminished following resolution of the pain. Of particular note the activation began to diminish in the third condition in contrast to the increased activation observed during the cluster headache attack in the CHA group (see Fig 7.2).

Hypothalamic Activation (CHI)

In the eight patients out of the active bout who did not experience a cluster headache attack, there was no significant activation observed in the region of the hypothalamic grey on comparing the HA*, No-CH and Rest Post-GTN conditions with Rest.

Differences Between the Two Groups (CHI and CHA)

Comparison of the conditions post - GTN/CHA and HA/CHI with rest*

With use of a group (CHA - CHI) - by - condition (post-GTN / HA* versus rest) interaction analysis, no significant differences were found between the groups.

Comparison of the conditions No-CH/CHI and CH/CHA with HA*/CHI and post-GTN/CHA

This comparison revealed greater activations for the CHA group, in the left insula, right inferior frontal cortex (BA47), and in the region of the basal vessels. Additionally activation in the CHA group was seen in the left ipsilateral (to the pain) hypothalamic grey area.

8.4 Discussion

Activation in this study was seen in two groups of structures:

- Areas involved in the processing of pain
- Extracerebral areas in the region of the intracranial blood vessels.

Pain-processing areas

Activation of areas associated with pain processing has been discussed in Chapter 7 (PET study 1). Activation of these regions was observed during the immediate and short-lived GTN-induced headache with resolution of the activation with the pain. The same pattern of activation has been observed during acute cluster headache and other different types and anatomical sites of pain e.g experimental tonic pain - heat, oesophageal stimulation, visceral, cold pressor, ethanol injection; clinical pain - migraine, mononeuropathy, angina, cancer-related pain; and, experimental phasic pain - heat and laser (Derbyshire & Jones, 1998). Activation of these regions therefore appears to be a response to a painful stimulus.

Areas Specific for Cluster headache

Patients out of the active bout did not experience a cluster headache attack following attempted triggering. Consistent with this there was no detectable activation of the

hypothalamus as seen during acute cluster headache, in any of the conditions following GTN administration, suggesting that activation of this region appears to be specific to the development of a cluster headache attack. This difference between the two groups was confirmed using the group-by-condition interaction analysis. It is therefore tempting to consider a trait change in the hypothalamus that is converted into a state change when the patient is in the active bout. The cited genetic observations and studies in Chapter 1, and supportive observation from Chapter 10- Study 4, suggest cluster headache occurs in genetically predisposed individuals. The consistent absence of hypothalamic activation in functional imaging studies of pain (Derbyshire & Jones, 1998), which include migraine, another clinically distinct primary and predominantly first division trigeminal pain syndrome (Weiller *et al.*, 1995), and secondary first division trigeminal pain (May *et al.*, 1998b), strongly support that activation of the hypothalamus in acute cluster headache is not a response to pain but specific to the primary pain syndrome of cluster headache. The cluster headache PET study by Hsieh and colleagues unfortunately did not include sufficient number of patients to address the issue of hypothalamic activation (n=4; 2 with right and 2 with left sided headache) (Hsieh *et al.*, 1996a). PET study 1 required at least 5 patients (with pain lateralised to the same side) before significant hypothalamic activation was observed. Moreover, subsequent to PET Study I and Study 2, specific structural change has been shown in the region of the hypothalamus in cluster headache patients compared to matched controls using voxel-based morphometric analysis of the pooled T1-weighted MRI scans performed on the patients in Study 1 and 2 (May *et al.*, 1999a).

Extracranial areas

In addition to the activation within the brain, activation was seen in the region of the intracranial vessels, in particular the region of the cavernous sinus. PET data cannot

distinguish between arterial and venous structures. Therefore the activation in the region of the cavernous sinus could be postulated to be due to increased venous inflow from the superior ophthalmic vein draining the ophthalmic artery or a longer transit time for the H_2O^{15} tracer in this region possibly due to impeded venous drainage. However, this region was subsequently further defined using magnetic resonance angiography (MRA) in a single-subject study during GTN-provoked cluster headache (May *et al.*, 1999b). Three angiograms were obtained at rest, after GTN inhalation and during the cluster headache attack. An image subtraction tool was used to compare angiograms in the three different conditions. Following GTN administration, but before the onset of cluster headache, there was dilatation of the basilar and both the internal carotid arteries compared to the baseline pain-free condition. These vessels however remained dilated into the third condition of GTN-induced cluster headache some 20 minutes later. In a volunteer study (i.e non-cluster headache sufferer) GTN induced carotid dilatation as measured by MRA was shown to have a short time course with resolution of the dilatation by the time of the third condition in the cluster headache patient. Thus, indicating that the attack itself maintains the dilatation after the effect of GTN has abated. This is similar to the activation pattern seen in the same regions with PET in condition 3 of PET study 1 and study 2. In the patient with spontaneous cluster headache a repeat study of spontaneous cluster headache imaged with MRA, as described, showed dilatation of the internal carotid artery ipsilateral to the pain. Both the PET and MRA findings are consistent with observations that spontaneous and GTN - provoked attacks are reported to be accompanied by a bilateral decrease in middle cerebral artery blood flow velocities implying vasodilatation (Dahl *et al.*, 1990). The data are also consistent with human and animal experimental data showing bilateral carotid artery dilatation and increase in cerebral and extracerebral blood flow with trigeminal (Goadsby & Edvinsson, 1994b; Goadsby *et al.*, 1986; Tran Dhin *et al.*, 1992)

and parasympathetic stimulation (Goadsby *et al.*, 1983); activation of both the trigeminal and parasympathetic pathways have been shown to occur in cluster headache (Goadsby & Edvinsson, 1994a). The specificity of the observed vascular changes to first division trigeminal pain was shown in an MRA study of 8 non-headache subjects during capsaicin injected separately into three sites, the forehead (1st division trigeminally mediated pain), the chin (3rd division trigeminally mediated pain) and the leg (non-trigeminally mediated pain). Significant bilateral vasodilatation of the intracavernous portion of the internal carotid artery was observed during capsaicin injected into the forehead but not following injection into the chin or leg (May *et al.*, 2001).

8.5 Summary

This study has shown that activation of the hypothalamus in cluster headache appears to be specific to this primary head pain syndrome and occurs only in relation to the acute cluster headache attack. Furthermore, the observed vascular changes may be epiphenomenal to activation of first division trigeminal pain fibres. The term neurovascular head pain is therefore proposed to give equal weight to the pathological and physiological mechanisms involved.

Table 8.2

Significant increases in blood flow in patients in (CHA) / out (CHI) of the bout during the scans defined for CH / HA* compared with rest

The activation is tabulated in terms of the activated brain regions and their Brodmann areas and the x, y and z coordinates to the standardised anatomical space and refer to the line joining the anterior and posterior commissures which is situated at 0mm. Each location is the peak within a cluster (defined as the voxel with the highest Z-score) $p < 0.001$

		In the bout (CHA) : CH versus rest				Out of the bout (CHI) : HA* versus rest			
Region	Brodmann areas	Talairach coordinates			Z score of peak activation	Talairach coordinates			Z score of peak activation
		x	y	z		x	y	z	
L Hypothalamus		-2	-18	-8	Z = 3.68				
R Anterior Cingulate cortex	BA 24	2	22	24	Z = 4.9	4	36	12	Z = 4.91
R Mid-Cingulate cortex	BA 24	4	12	28	Z = 4.65	-2	12	22	Z = 4.65
L frontal lobe	BA 10	-24	42	12	Z = 3.81	-20	56	6	Z = 4.77
L Insula		-40	12	-8	Z = 4.37	-28	20	-6	Z = 3.92
R Insula		32	10	2	Z = 4.28	32	-10	10	Z = 3.9
R Thalamus		6	-12	6	Z = 5.01	10	-8	4	Z = 3.47
L Basal ganglia		-20	-12	2	Z = 4.22	-12	14	8	Z = 4.22
R inferior frontal cortex	BA 47	48	30	-20	Z = 4.08				
L SM area	BA 6	-60	20	2	Z = 4.19				
R frontal lobe	BA 10					18	60	10	Z = 4.25
L temporal lobe	BA 42					-52	-22	6	Z = 5.17

CHAPTER 9

PET Study 3 - Co-existent Migraine and Cluster Headache

9.1 Introduction

The diagnosis of idiopathic or primary headache syndromes has been based on bedside methods, history and physical examination, in the absence of any known tests based on disease biology. Recent observations with PET have identified the brain stem in migraine (Weiller *et al.*, 1995) and, from the studies presented in this thesis, the region of the posterior hypothalamic gray matter in cluster headache (May *et al.*, 1998a) to be specifically activated in these disorders. These regions are, therefore, candidates to differentiate the pathophysiology of these syndromes and provide anatomical and functional insights into their pathogenesis.

The International Headache Society has provided clinical diagnostic criteria for most primary head and facial pain syndromes (Headache Classification Committee of the International Headache Society, 1988). These have served to minimise inter-observer diagnostic variability and provide homogeneous patient groups for the study of pathophysiological processes. The current classification system allows the co-existence of more than one primary headache syndrome within an individual, providing operational diagnostic criteria that have been widely applied. Neuroimaging results and clinical observations have lead to one of the most crucial questions in headache biology; whether discrete syndromes as clinically classified can be differentiated biologically. A corollary would be whether that information could eventually be exploited in any useful diagnostic or therapeutic role.

Nitroglycerine has been shown to provoke attacks of migraine (Iversen *et al.*, 1989; Olesen *et al.*, 1994; Sicuteri *et al.*, 1987) and cluster headache during the active bout

(Ekbom, 1968). We present in detail the case of a patient with co-existent migraine and episodic cluster headache, as defined by IHS classification criteria, who was imaged during an active bout of cluster headache to further address the pathophysiology of the syndrome. However, following administration of GTN he experienced a typical migraine headache. The headache was accompanied by lateralised brainstem activation as observed by Weiller and colleagues (Weiller *et al.*, 1995) but no activation was seen in the region of the hypothalamus, supporting the concept that dysfunction of specific regions of the brain are unique findings for individual primary head pain syndromes.

9.2 Methods

Case Report

A 43-year-old man had been under the care of the National Hospital for Neurology and Neurosurgery for management of episodic cluster headache. He gave a history of attacks of excruciating mainly right-sided retro-orbital and frontal pain from the age of 18 years. Ipsilateral to the pain there was lacrimation, conjunctival injection, drooping and swelling of the eye-lid, nasal congestion and rhinorrhoea. He was invariably restless during the attacks. The attacks lasted between 30-45 minutes and occurred up to three times a day for 4-5 weeks at a time every 1-4 years, usually in May or October. He rarely drank alcohol which he always avoided during a bout. He obtained effective abortive relief from acute attacks with subcutaneous sumatriptan. The patient also gave a history since the age of 14 years of attacks of generalised throbbing severe headache, exacerbated by movement and accompanied by photophobia and phonophobia. The attacks would last about 2 days and had occurred once every 1-3 weeks since onset. Notably during an active bout of cluster headache he continued to experience such attacks at a similar frequency and usually after an attack of cluster headache. Apart from a long-standing history of lower back pain, the past medical history was

unremarkable and clinical examination had always been normal. Neuroimaging with computerised tomography had also been normal.

Study Design

The patient presented in the second week of an active bout of cluster headache. The total duration of the bout proved to be longer than usual lasting 3 months. He had been experiencing one cluster headache attack a day lasting 30-40 minutes without treatment. He was not taking any prophylactic therapy. The patient was studied with PET following administration of 1.2-mg sublingual GTN. Our previous study design was followed (PET Study 1). Twelve consecutive scans were obtained during the baseline rest condition, after administration of GTN, during the induced-headache attack and after treatment of the attack with 6mg subcutaneous sumatriptan. For each scan the patient rated headache intensity with a 0-10 visual analogue scale (VAS 0-no pain; 10-maximum intensity). The patient had his eyes closed at all times during scanning.

Data Analysis

The data were analysed as detailed in PET Study 1. In addition a correlation analysis was done seeking to address whether there were brain areas in which activity varied as a function of pain intensity.

9.3 Results

At the start of the study the patient commented on a mild right-sided hemi-cranial background ache (VAS 1/10) without autonomic symptoms, which had been present between his attacks of cluster headache since the start of the current bout (condition 1 - rest). Three scans were performed at rest. Within 10 minutes of GTN administration the patient experienced a mild bitemporal throbbing headache which subsequently

increased in severity (maximum VAS score 9/10), and was accompanied by photophobia and phonophobia which he described as typical of his migraine attacks and consistent with IHS criteria (condition 2- migraine headache). Six scans were performed during the migraine headache. Following 6mg subcutaneous sumatriptan the pain settled to baseline level with improvement of the photophobia and phonophobia for the remaining 3 scans (condition 3 – post-sumatriptan). Of note the patient began to complain of moderately severe low back pain (VAS 6) from being prostrate in the scanner during acquisition of the final two scans.

Regional activation during headache

Cortical and Subcortical activations

First, there was activation of the rostral brainstem, slightly lateralised to the left (Figure 8.1). Secondly, there was activation of the anterior and posterior cingulate cortices, the prefrontal, posterior insular and cerebellar cortices bilaterally, the left thalamus and superior parietal cortex, and the right supplementary motor cortex and right lentiform nucleus (Table 9.1 and Figures 9.2).

Extracranial Activations

Thirdly, there was a strong bilateral activation of structures outside the brain corresponding to the region of the large intracranial blood vessels (Table 9.1 and Figure 9.3).

Correlation Analysis

The visual analogue score was correlated with the adjusted rCBF at each voxel and the profile of correlation coefficients constituted into a statistical parametric map. This showed that the activations of the intracranial blood vessels (Figure 9.3), the anterior

cingulate cortex and the prefrontal cortices bilaterally were strongly correlated with pain intensity ($p < 0.001$).

Regional activation following treatment with sumatriptan

Cortical and Subcortical activations

Comparing the post-sumatriptan condition with rest, strong activation of the rostral brainstem on the left persisted following successful treatment of the headache. Moreover, activity increased further during the post-sumatriptan condition in the brainstem (Figure 9.4). There was activation bilaterally of the prefrontal and cerebellar cortices, on the left of the thalamus and the superior parietal cortex, and on the right of the anterior and posterior cingulate cortices, the posterior insula, the supplementary motor cortex and the primary somatosensory cortex (Table 9.2).

Extracranial Activations

Notably, there was no activation in the region of the intracranial blood vessels after resolution of the headache (Table 9.2 and Figure 9.4).

9.4 Discussion

In this study we have observed the pattern of brain activation during migraine in a patient who coincidentally was a cluster headache sufferer, but who did not experience a cluster headache during the scan despite being in an active cluster headache period. The study demonstrates that the brain activation pattern is as distinct as the clinical picture even when these syndromes occur in the same individual. Furthermore, pooling of tracer in the large intracranial vessels, consistent with that reported in cluster headache (PET Study1) demonstrates a fundamentally neurovascular, as opposed to vascular, nature of pain expression in migraine.

Genetic predisposition

The genetic basis of migraine has been supported by numerous studies (Ferrari, 1998). Familial hemiplegic migraine is an autosomal dominant condition. Fifty-five percent of cases are due to mis-sense mutations in the α_1 subunit of the P/Q type-voltage gated calcium channel on chromosome 19 (Ophoff *et al.*, 1996). A further 15% of cases have been localised to a locus on chromosome 1 (Ducros *et al.*, 1997) and the remainder as yet remain unaccounted for. Furthermore abnormalities on chromosome 19 may account in part for genetic susceptibility in patients with more common migraine with and without aura (May *et al.*, 1995). The genetic basis for cluster headache has been discussed in Chapter 1.

Co-existence of migraine and cluster headache

The prevalence rate of cluster headache is estimated between 0.07 and 0.2% (D'Alessandro *et al.*, 1986), and that of migraine in the UK is 12-15%, with a one year prevalence of 7% for males (Steiner *et al.*, 1999). Most series show that the age of onset of cluster headache is later than for migraine, and in the majority of individuals attacks of migraine stop following the onset of cluster headache (Andersson, 1985; Kudrow & Kudrow, 1994; Solomon & Cappa, 1986). The two conditions can occur simultaneously (Solomon & Cappa, 1986); and although it has been suggested that migraine does not occur during a cluster period (D'Amico *et al.*, 1997), there are reports of attacks occurring exclusively during this time (Kudrow & Kudrow, 1994).

Our patient provides the ideal situation in which to test the hypothesis that migraine and cluster headache can be distinguished biologically by differential involvement of regions of the central nervous system.

Triggered and spontaneous attacks of migraine and cluster headache

Variable attack duration and availability of the appropriate investigative facilities confound investigating spontaneous attacks of cluster headache and migraine when attacks occur. Triggering attacks can circumvent this problem. Nitroglycerine triggered attacks of cluster headache have been shown to be clinically (Ekbom, 1968) and experimentally (Fanciullacci *et al.*, 1997) identical to spontaneous attacks (Goadsby & Edvinsson, 1994a). Attacks of migraine without aura can also be triggered with nitroglycerine and such an approach is well validated (Iversen *et al.*, 1989; Olesen *et al.*, 1994). Thomsen and colleagues (Thomsen *et al.*, 1994) demonstrated that following an intravenous infusion of nitroglycerine, 10 individuals with a history of migraine without aura experienced headache immediately during an infusion. The headache met IHS criteria for migraine in one patient. The immediate headache persisted in most individuals and was followed by a delayed more severe headache 3-10 hours later. The delayed headache was identical to the spontaneous migraine attacks and consistent with IHS criteria in 8 of the 10 cases. In keeping with this study, our patient developed a migraine attack without aura typical of his spontaneous attacks following the administration of nitroglycerine.

Brainstem activation in migraine headache

In 1995 Weiller and colleagues (Weiller *et al.*, 1995) reported brainstem activation during a PET study of 9 individuals during spontaneous attacks of migraine without aura. Importantly, the activation persisted after acute treatment with subcutaneous sumatriptan had induced relief from pain and associated symptoms, suggesting that the role of the activation was not simply limited to an anti-nociceptive response. Our finding reproduces this observation and refines it anatomically to the dorsal rostral pontine region. The finding of rostral brainstem activation is consistent with the clinical

observations reported by Raskin and colleagues (Raskin *et al.*, 1987) and later reproduced by Veloso and colleagues (Veloso *et al.*, 1998), of migraine and migraine-like headache in predominantly headache-free individuals following electrode implantation into the brain stem. It is also consistent with the case report of migraine associated with a plaque of multiple sclerosis in the rostral brainstem reported by Haas and colleagues (Haas *et al.*, 1993). Taken together these studies point to the rostral brainstem as a possible site for neurobiological dysfunction in migraine.

Activation of structures involved in the processing of pain

Activation of the structures associated with pain processing observed in this study (thalamus, cingulate cortex, insula, prefrontal cortex, supplementary motor cortex, primary somatosensory cortex, cerebellum and basal ganglia) have been discussed in PET Study 1 (See Tables 9.1 and 9.2). In addition activation was observed in the posterior cingulate cortex (BA23) which has strong connections with the superior parietal cortex (BA7) where visual information is integrated and may be responsible for the emotional response to a visual target (Derbyshire & Jones, 1998; Hsieh *et al.*, 1995; Hsieh *et al.*, 1996a; Iadarola *et al.*, 1998). The patient's eyes were open in between scanning but closed during scanning.

Prominent activation of the aforementioned structures was observed during the acute attack of migraine. Residual activation of certain structures following treatment of the migraine headache with sumatriptan may be attributed to the continuing processing of pain experienced from the lower back during acquisition of the final scans.

Activation of the cranial vessels

Activation of structures outside the brain corresponding to the cranial vessels has been observed during both primary and secondary first division trigeminal head pain. These structures were activated during acute attacks of nitroglycerine-induced and spontaneous cluster headache (PET Study 1) and found subsequently by magnetic resonance angiography to be the carotid arteries (May *et al.*, 1999b). The same finding has been shown in secondary head pain induced by capsaicin injected into the forehead (May *et al.*, 2001; May *et al.*, 1998b). Consistent with this finding the patient in this study shows strong activation in the region of the carotid arteries during the migraine headache, but not following resolution of the attack. Furthermore, this activation is strongly correlated with his headache intensity rating (Figure 9.3), which is compatible with blood flow velocity changes measured in middle cerebral artery with transcranial Doppler during nitroglycerine-induced headache and spontaneous attacks of migraine (Thomsen *et al.*, 1995; Thomsen *et al.*, 1994).

9.5 Summary

Our study demonstrates that in a patient who, crucially, suffers from two types of primary headache, migraine and cluster headache, the attack phenomenology predicted the appropriate brain activation pattern. Three groups of structures were activated during migraine headache: 1) a migraine specific region in the brain stem, 2) regions associated with pain processing, and 3) the cranial blood vessels. The vascular changes observed are in keeping with the general principle that when the first division of the trigeminal nerve is stimulated, neurally mediated vascular change ensues that is not specific to the primary headache type. Furthermore, the attacks as observed when triggered by a nitric oxide donor are both clinically, and by brain imaging, identical to spontaneous migraine. These data contribute strongly to the view that both migraine and

cluster headache are essentially disorders of the central nervous system that share a pain pathophysiology but are also pathogenically distinct.

Table 9.1

Regional increases in Blood Flow during Migraine headache compared to Rest

Region	Talairach Co-ordinates			Z score of peak activation
	x	y	z	
Left thalamus	-12	-4	10	3.8
Anterior cingulate cortex BA24/32	0	30	18	3.87
Posterior cingulate cortex BA23	0	-30	26	4.17
Right prefrontal cortex BA10	30	38	22	3.75
Left prefrontal cortex BA10	-30	44	24	3.33
Right supplementary motor cortex BA6	4	-6	64	3.77
Left superior parietal cortex BA7	-4	-70	42	4.58
Right lentiform nucleus	22	-6	8	3.66
Right posterior insula	28	-26	0	3.34
Left posterior insula	-34	-30	0	3.57
Right cerebellum	46	-64	-34	3.39
Left cerebellum	-26	-68	-22	5.07
Left dorsal rostral pons	-2	-28	-22	3.32
Intracranial vessels	0	-12	-32	3.89
Intracranial vessels	-40	6	-18	4.49
Intracranial vessels	48	16	-26	4.45
Intracranial vessels	54	28	-22	4.49
Intracranial vessels	-46	24	-24	3.89

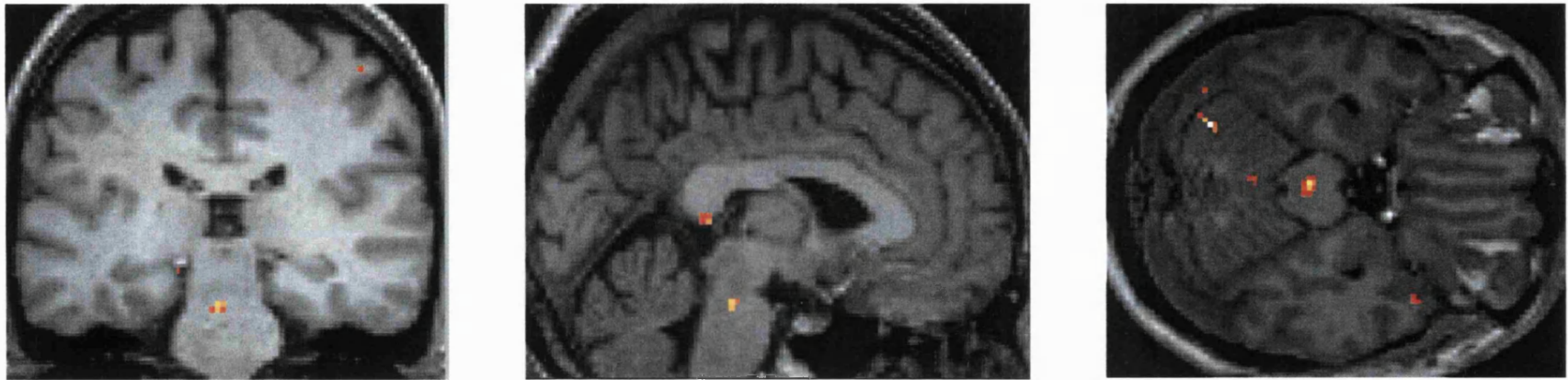
The activation is tabulated in terms of the activated brain regions and their Brodmann areas and the x, y and z coordinates to the standardised anatomical space and refer to the line joining the anterior and posterior commissures which is situated at 0mm. Each location is the peak within a cluster (defined as the voxel with the highest Z-score) $p < 0.001$

Table 9.2**Regional increases in Blood Flow Post-sumatriptan compared to Rest**

Region	Talaraich Co-ordinates			Z score
	x	y	z	
Left thalamus	-10	-6	2	4.13
Right anterior cingulate cortex BA24/32	14	38	0	4.45
Right posterior cingulate cortex BA23	6	-36	32	3.79
Right posterior insula	40	-22	2	4.19
Right prefrontal cortex BA9	22	36	32	4.45
Left prefrontal cortex BA9	-26	30	28	3.83
Right supplementary motor cortex BA6	6	-16	52	4.08
Right primary somatosensory cortex BA1	60	-22	42	5.05
Left superior parietal cortex BA7	-4	-70	44	4.49
Right cerebellum	40	-64	-44	4.22
Left cerebellum	-38	-72	-24	3.53
Left dorsal rostral pons	-2	-28	-22	4.22

The activation is tabulated in terms of the activated brain regions and their Brodmann areas and the x, y and z coordinates to the standardised anatomical space and refer to the line joining the anterior and posterior commissures which is situated at 0mm. Each location is the peak within a cluster (defined as the voxel with the highest Z-score) $p < 0.001$

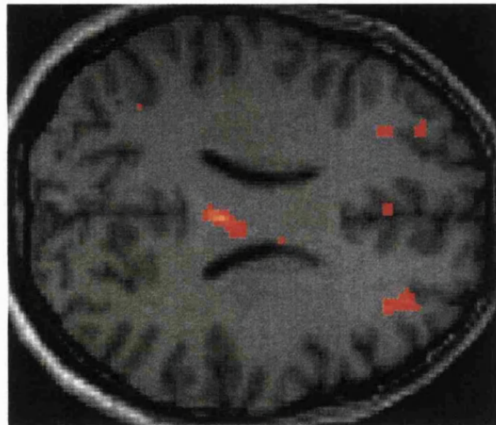
Figure 9.1
Dorsorostral Brainstem Activation during Migraine Headache compared to Rest



Activations during the attack are shown as statistical parametric maps that show areas of significant rCBF increases ($p < 0.001$) in colour superimposed on an anatomical reference derived from a T1-weighted MRI. The left side of the picture is the left side of the brain.

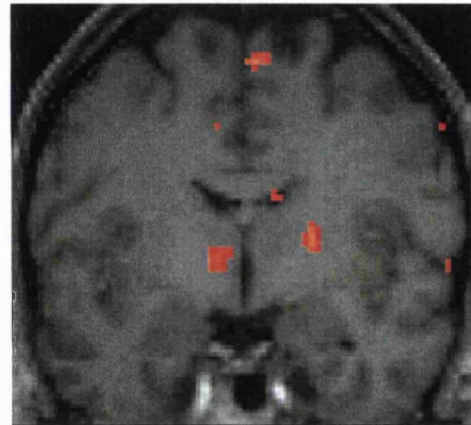
Figure 9.2

Cortical and Subcortical Activations during Migraine headache compared to Rest



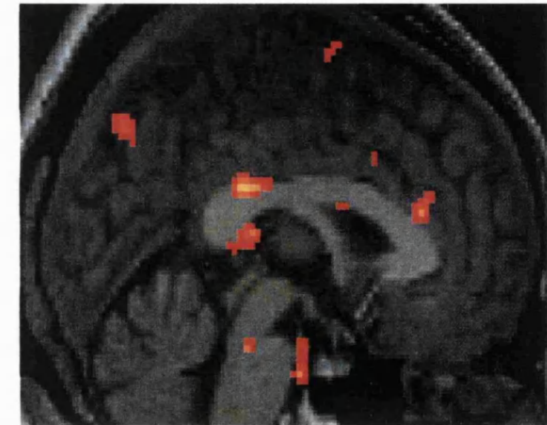
A

Posterior cingulate and bilateral
prefrontal cortices



B

Right thalamus, left lentiform
nucleus and the superior parietal
cortex



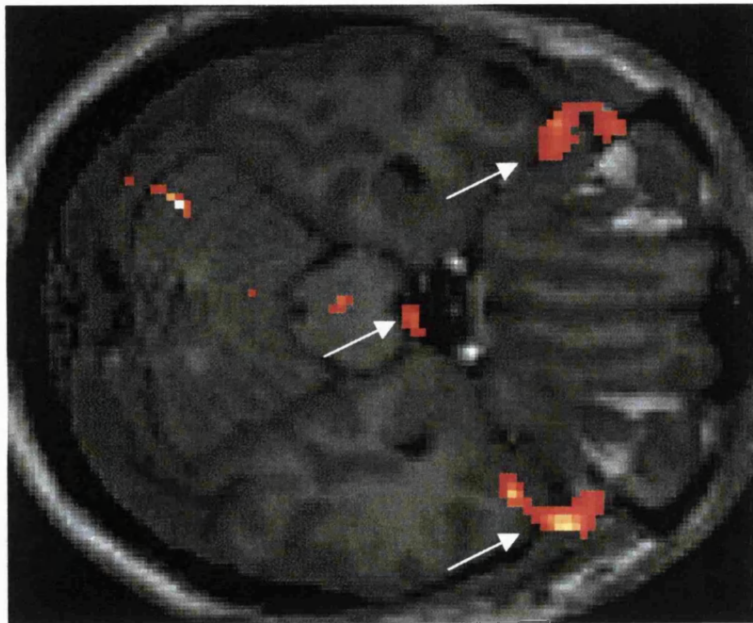
C

Anterior and posterior cingulate,
superior parietal cortices,
dorsorostral brainstem and cranial
vessels

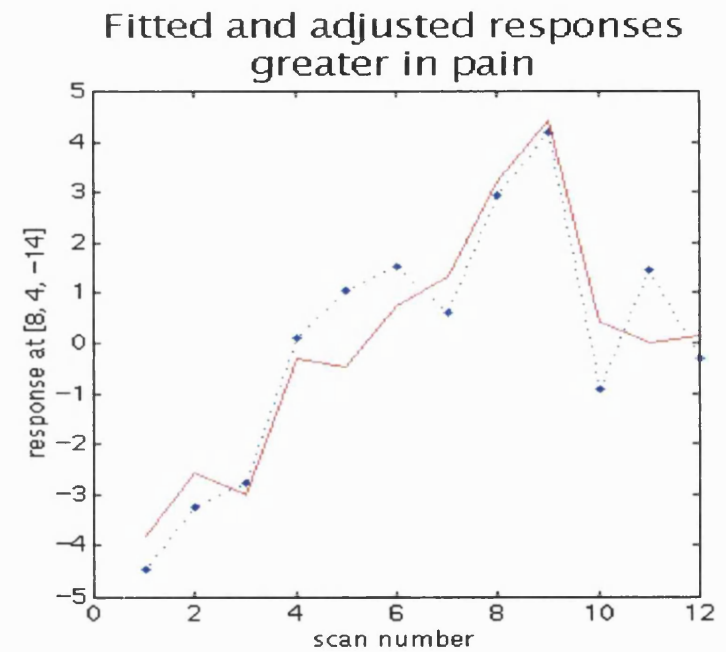
Activations during the attack are shown as statistical parametric maps that show areas of significant rCBF increases ($p < 0.001$) in colour superimposed on an anatomical reference derived from a T1-weighted MRI. The left side of the picture is the left side of the brain.

Figure 9.3

Activation of the Intracranial Vessels during Migraine Headache compared to Rest



A



B

The figure demonstrates strong bilateral activation of structures outside the brain (arrowed) corresponding to the region of the large intracranial blood vessels (A). The visual analogue score (blue dotted line) was correlated with the adjusted rCBF at each voxel (red line) and the profile of correlation coefficients constituted into a statistical parametric map (A). This showed that the activations of the intracranial blood vessels closely tracked the patients pain (B).

Figure 9.4

Activation pattern of the dorsorostral brainstem and intracranial vessels in the three conditions of interest

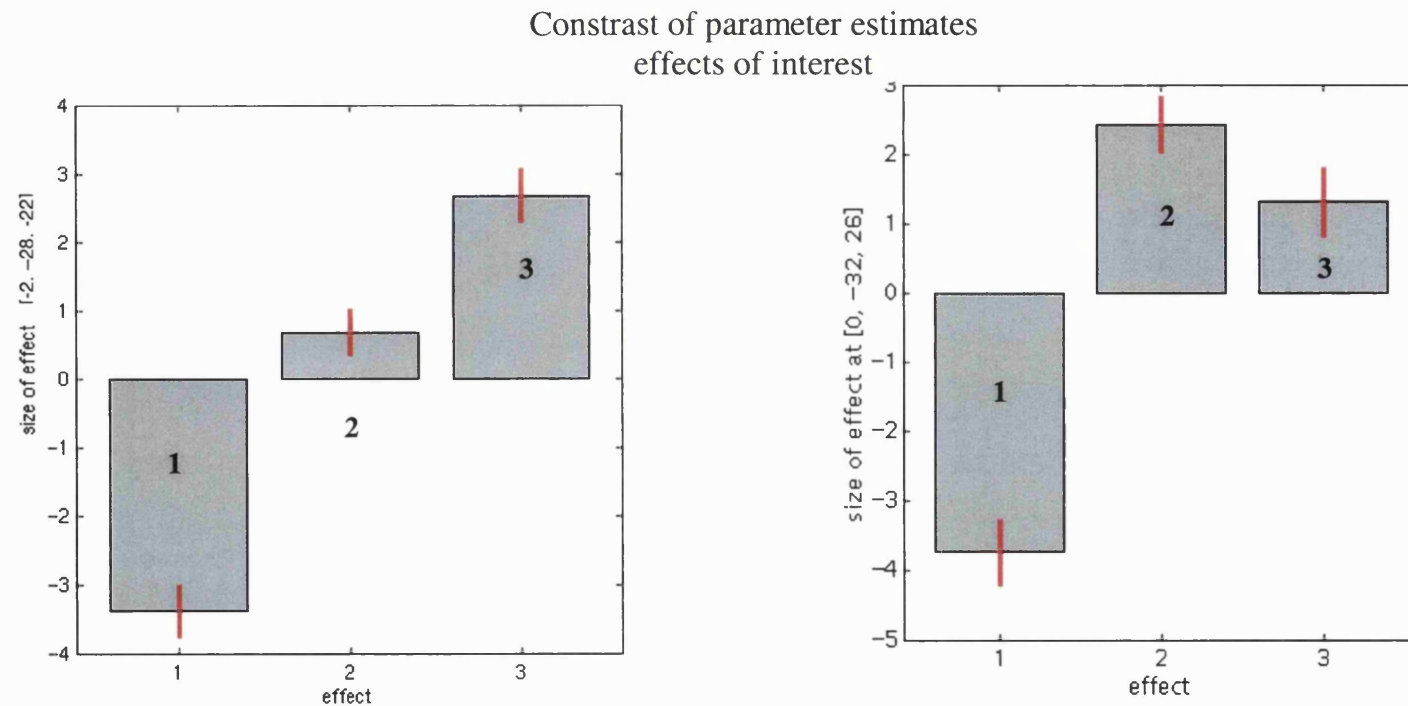


Figure A shows the activation pattern in the region of the dorsorostral brainstem, and Figure B the activation pattern in the region of the intracranial vessels, in the three conditions of interest. The Y-axis indicates the activation in terms of Z score and the X-axis the conditions of interest: Condition 1 – Rest, 2 – Migraine Headache, 3 – Post-sumatriptan. The red line indicates the 95% confidence intervals.

PART 3

A CLINICAL STUDY OF CLUSTER HEADACHE

CHAPTER 10

Cluster Headache : A Prospective Clinical Study of 230 Patients

10.1 Introduction

Recruitment of patients to participate in the described PET studies also enabled prospective study of the clinical and epidemiological characteristics of a large mainly non-clinic based population of cluster headache sufferers. Characteristics of the syndrome and patient group, diagnostic accuracy and management strategies in clinical practice were addressed.

10.2 Methods

The study group included cluster headache volunteers from two national support groups and patients referred to the National Hospital for Neurology and Neurosurgery between 1997 and 1999. Patients from National Support Groups, the Migraine Trust and Migraine Action Association, were recruited through quarterly support group newsletters and direct mailing. Only patients diagnosed with cluster headache according to the criteria of the Headache Classification Committee of the IHS (digit code 3.1 and 3.3) were included in the sample group presented.

The information was compiled from a standardised questionnaire. Information was collected by telephone and direct consultation. To ensure a consistent basis for the clinical comparisons all patients were interviewed by myself ; selected patients were in addition interviewed by a second researcher (Professor P J Goadsby or Dr Arne May, Research fellow) to ensure a definitive diagnosis and accurate collection of the clinical data.

Results were assembled in a database (Microsoft Access) which was queried for particular issues. The results were statistically evaluated using a Chi-squared analysis with significance level set at $\alpha = 0.05$.

10.3 Results

10.3.1 Sample Group

The sample group comprised 230 cluster headache sufferers. Seventy-six percent were recruited through national support groups and 24% from the National Hospital for Neurology and Neurosurgery. Seventy-two percent were men and 28% women, giving a M:F ratio of 2.5:1. Seventy-nine percent suffered from episodic cluster headache (ECH) and 21% with chronic cluster headache (CCH). Of the latter group 13% suffered from primary CCH, whereby the symptoms had been unremitting from onset, and 8% secondary CCH, having evolved from an initially episodic pattern. Of the ECH group 3% had evolved from primary CCH. The mean age of onset of ECH was 28.4 years (M 29.5, F 25.7 years), while that of CCH was later at 37 years (M 33.9, F 44.1 years). The youngest age of onset was 6 years and the oldest 67 years. Incidence diminished with age in men and women.

10.3.2 Clinical Characteristics- attacks

Site of Pain: The site of pain was predominantly retro-orbital (92%) and temporal (70%). However, the pain was experienced over a wide area including the forehead, jaw, cheek, upper and lower teeth, and less commonly the ear, nose, neck, shoulder and other regions of the hemicranium (Table 10.1). Thus the pain was predominantly in the distribution of the first division of the trigeminal nerve.

Side of Pain: The pain was strictly unilateral in all the individuals. A greater number experienced right-sided attacks (60%; Table 10.2). In the ECH group 14% had experienced a side shift only within the same bout, while 18% had experienced attacks on one side during one bout with a side shift in a subsequent bout. Only 3% had experienced side changes within a bout *and* symptoms exclusively on one side during one bout and the other side during a subsequent bout. No patient experienced pain occurring simultaneously on both sides during an attack, but two patients had experienced a side shift side within the same attack.

Associated features: Lacrimation was the most consistently reported autonomic feature, followed by conjunctival injection, nasal congestion, ptosis/eye-lid swelling and rhinorrhea (Table 10.3). Fifty percent of individuals reported nausea during the acute attack and a similar number reported at least one of photophobia (56%) and phonophobia (43%), and less commonly osmophobia (26%; Table 10.4). Ninety-three percent reported that they were restless during the attacks or that movement did not exacerbate the pain.

Aura symptoms: Fourteen percent reported symptoms consistent with migraine aura associated with the cluster headache attack (12F, 21M). The symptoms in most occurred either during, or within 60 minutes before or after the cluster headache attack. Seventy percent of this group experienced visual symptoms, 16% hemi-motor and 13% hemi-sensory symptoms, 1% experienced both visual and hemi-sensory symptoms. Thirty-six percent who experienced aura associated with the attack had a history of migraine with (40%) and without (60%) aura; 15% who did not give a history of migraine, had a family history of migraine.

Periodicity: The mean maximum attack duration was 159 minutes and mean minimum attack duration 72 minutes (Table 10.5). The mean maximum number of attacks within a 24-hour period was between 4 and 5. Most individuals experienced one bout every year. The range of bout frequencies is given in Figure 10.1. The longest reported remission period was 20 years. The mean bout duration was 8.6 weeks. Forty-three percent of individuals commented upon a seasonal propensity of bout onset (ECH) or exacerbation of symptoms (CCH). This occurred most commonly in spring and autumn. Most patients reported predictability of attack onset nocturnally (73%), waking them from sleep, and less so during the day (37%).

10.3.3 Clinical characteristics - patients

Episodic versus Chronic cluster headache: The clinical differences between chronic and episodic cluster headache are few (Tables 10.1-10.5). Individuals with chronic cluster headache are more likely to report radiation of the pain to the upper teeth, jaw, cheek, ear and shoulder. Rhinorrhoea is not as consistent an accompaniment as in ECH and osmophobia was more commonly reported. Side change within the same 'bout' was more commonly reported in the CCH group. Although attack frequency was similar to the ECH group, the attack duration reported was shorter in the CCH group.

History or Family of Migraine and Cluster Headache: Twenty-six percent of cluster headache sufferers reported a past history of migraine (40% F, 21% M). The age of onset of migraine was earlier than that for cluster headache in most individuals. Thirty-three percent of sufferers gave a family history of migraine (parents and/or siblings). Five percent gave a history of cluster headache in a parent or sibling (diagnosed or typical witnessed clinical description). Three individuals (1%) gave a family history of

cluster headache in more than one family member suggestive an autosomal dominant pattern of inheritance.

Social habits: The majority of patients were smokers (67%) or had been smokers in the past (17%). None of those who had stopped smoking noted cessation or any change in pattern of their symptoms. Ninety percent of patients who drank alcohol reported sensitivity with triggering of an attack during the active bout.

10.3.4 Cluster headache in Women

An overall male to female ratio of 2.5:1 was observed. The ratio was consistent when addressed by decade of onset of cluster headache (Table 10.6). There were few significant differences in clinical characteristics between men and women (Tables 10.1-10.5). The onset of cluster headache in women occurred later than puberty in the majority of women. Of the 65 women cluster headache started around the time of puberty in 11%. In these individuals there was no predilection for the syndrome to start before or after menarche.

Oral contraception and pregnancy: Thirty-four percent had been on an oral contraceptive preparation (OCP) following onset of the syndrome and none reported an effect on their symptoms whilst on this. Of those symptomatic during childbearing years (91% had onset of symptoms \leq 50 years of age) only 5% experienced cluster headache attacks during pregnancy. Five percent commented that they were due for a bout when they became pregnant but missed the bout. In one case the bout started post-partum on two occasions.

Menses, menopause and HRT: Only one sufferer with CCH commented on worsening of symptoms in relation to menstruation; she also gave a history of migraine. Onset of cluster headache occurred at the same time as the menopause in 3%. In addition one woman who had a 28-year history of ECH commented that she had experienced one of her longest bouts during the menopause. However, of a further 26% who were experiencing cluster headache bouts at the time of the menopause, there was no change in the pattern of symptoms. Of 22% who were on HRT none reported change of symptoms as a result of starting or stopping replacement therapy.

10.3.5 Accuracy and Rapidity of Diagnosis

The most notable observation is the reduction in mean time to diagnosis by decade of onset (Table 10.6). A neurologist has diagnosed at least half of the sufferers (Figure 10.2). The number diagnosed by a neurologist has shown a general trend to increase through the decades, although the figures for individuals with onset of symptoms before 1960 include only a small number of patients. These are viewed with caution (Figure 10.3). Despite this, and a more rapid time to diagnosis, the mean number of general practitioners seen prior to diagnosis has not changed and at least two-thirds of sufferers have been seen previously by another specialist (Table 10.6). Dentists and Ear, Nose and Throat (ENT) surgeons are most commonly consulted prior to neurological referral (Table 10.7). Fifty-two percent of sufferers who had been seen by a dentist or ENT surgeon had an invasive procedure performed for the pain. Notably 13% of sufferers have self-diagnosed with subsequent medical confirmation (Figure 10.3); this has been assisted by national support group information and more recently by information about cluster headache through the Internet. The small number diagnosed by a Migraine clinic is most likely due to the paucity of such clinics in the United Kingdom. Twenty-nine percent had had a CT head scan, 18% a MRI head scan and 11% both. There was no

significant difference in time to diagnosis, practitioners seen and diagnostic accuracy between men and women.

10.3.6 Treatment Regimens

Acute attack treatments: Less than half of the sufferers (45%) had been given the opportunity to try subcutaneous sumatriptan, while a greater proportion (61%) had tried the oral preparation. The relatively recently available intranasal preparation had been tried by a small number (14%) of individuals (Table 10.8). Oral sumatriptan was the most commonly tried acute-relief treatment followed by an ergotamine derivative (56%). Many sufferers had not had the opportunity to try high flow oxygen. A large proportion of individuals had financed costly alternative therapy (63%) (Table 10.10). None had found alternative therapy consistently effective.

Preventative management: Preventatives established in the treatment of cluster headache had been prescribed to patients in similar proportion to those used in the treatment of migraine (Table 10.9). Although a larger proportion of CCH sufferers had been prescribed verapamil, corticosteroids, lithium, or methysergide, there was no statistically significant difference in prescribed prophylactic treatment between ECH and CCH sufferers. Similarly there was no difference in prophylactic agents prescribed to women compared to men with the exception of a β -blocker.

10.4 Discussion

These data are the first large-scale prospective, non clinic-based study of cluster headache. The study confirms the clinical phenotype: an episodic, very severe unilateral trigeminal pain with cranial parasympathetic autonomic symptoms. It provides evidence for a substantial and important change to the IHS diagnostic criteria proposing the

addition of agitation with no pain exacerbation with movement, as a further key differential feature with migraine. The data establish the fact that typical migrainous aura can be seen in cluster headache, and that cluster headache is indeed seen in females, perhaps more commonly than has been previously considered without any significant hormonal influences. Furthermore, the data highlight the issue of diagnosis and management of cluster headache outside neurological practice. There are unacceptably long delays to diagnosis and treatment with strategies that lack evidence of efficacy.

10.4.1 Clinical characteristics

The clinical characteristics of cluster headache in this study are entirely in keeping with earlier larger published series (Ekblom, 1970a; Friedman & Mikropoulos, 1958; Kudrow, 1980; Lance & Anthony, 1971; Manzoni *et al.*, 1983b; Sutherland & Eadie, 1972). There were few differences between ECH and CCH. Side change within the same 'bout' may be expected in individuals with longer duration of symptoms. With regard to the shorter attack duration in CCH it may be postulated that accuracy of attack duration is more likely in ECH than CCH. The former group usually enters a bout and then obtains a prescription for treatment, allowing adequate opportunity to assess attack duration. Individuals with CCH may have not left an attack untreated for some time and therefore are more likely to misjudge attack duration. This is borne out by a recent placebo-controlled study evaluating the efficacy of oral zolmitriptan in the treatment of cluster headache attacks which showed a high placebo response rate in the CCH group (Bahra *et al.*, 2000). An atypical syndrome of cluster headache has been reported in women (Lovshin, 1961; Peatfield *et al.*, 1982), the clinical features in this study were similar in men *and* women.

Migrainous aura: Aura symptoms have been described in association with the acute cluster headache attack (Duvoisin *et al.*, 1961; Lance & Anthony, 1971; Olesen, 1977; Sutherland & Eadie, 1972) in at least 6% of sufferers (Silberstein *et al.*, 2000), and with chronic paroxysmal hemicrania in a recent report (Matharu & Goadsby, 2001). In our series 36% of individuals who described aura gave a history of migraine; 40% had had migraine with aura and 60% migraine without aura. Of those who gave no past history of migraine 15% had a family history of migraine. Migraine assessed by proband report has been shown to be inadequate for diagnosing migraine in relatives, therefore this figure is likely to be underestimated by about 50% (Russell *et al.*, 1996). It may be hypothesised that migraine aura occurs in patients who carry an *aura-susceptibility* gene, probably closely structurally or functionally related to the migraine headache gene.

10.4.2 Cluster headache and women

Male:Female ratio: The M:F ratio of 2.5:1 is much lower than that previously published. The M:F ratio in the larger published series has varied between 3.2-7.1:1 (Andersson, 1985; Ekbom & Waldenlind, 1981; Klapper *et al.*, 2000; Krabbe, 1986; Kudrow, 1980; Lovshin, 1961; Manzoni, 1998). One of the largest series which has addressed the M:F ratio by decade of onset showed a gradual reduction of the ratio with time (Manzoni, 1998). However, our study shows that the ratio has been remarkably consistent through the decades (Table 10.6). This incongruity between studies can be attributed to the difference in cluster headache populations studied. The population studied by Manzoni and colleagues (Manzoni, 1998) was clinic-based. A fall in M:F ratio from 6.2:1 was reported for patients with onset of cluster headache before 1960 to 2.1:1 for those individuals with cluster headache onset between 1990-95 (total M:F ratio 1:3.5). This was accompanied by a corresponding reduction in M:F ratio for smoking

and employment rate consistent with population-based statistics. The consistent ratio by decade observed in our study is from a mainly non-clinic based group of cluster headache sufferers. It seems more probable that the change in ratio is a reflection of patient referral patterns to secondary and tertiary healthcare. Coupled with the increasing number of working women contributing to household incomes, it seems plausible that women are more likely now to seek treatment.

Clinical characteristics of cluster headache in women

This study found no clinical difference in the syndrome of cluster headache between men and women. Despite previous reports to suggest otherwise (Lovshin, 1961; Peatfield *et al.*, 1982), this observation has been confirmed by a recent retrospective study of 101 patients of which 32 were women (Rozen *et al.*, 2001).

The effect of 'female hormone- related events and cluster headache

Unlike migraine (Granella *et al.*, 1993), there does not seem to be a strong relationship between female hormones and cluster headache. Although this will only be adequately addressed in prospective longitudinal studies, there is no definite relation with menarche, the oral contraceptive pill, menstruation, menopause or HRT. This is supported by previous observations (Ekbom & Waldenlind, 1981; Horton, 1941), although occasional reports of exacerbation with menstruation have been documented observations (Ekbom & Waldenlind, 1981; Peatfield *et al.*, 1982). Typical cluster headache can occur during pregnancy, but it has been proposed that women with cluster headache report remission during pregnancy and recurrence of symptoms a few days after childbirth (Ekbom & Waldenlind, 1981). This is supported in this study and is consistent with observations in migraine suggesting some hormonal protective mechanisms during pregnancy.

10.4.3 Genetics, Cluster Headache and Migraine

Cluster headache has generally been thought to be without a genetic predisposition. Five percent of our patients, however, gave a family history of cluster headache. A positive family history has been reported in 1.9-10 % of patients with cluster headache (Klapper *et al.*, 2000; Kudrow & Kudrow, 1994) and there have been reports in monozygotic twins (Couturier *et al.*, 1991; Roberge *et al.*, 1992; Sjaastad *et al.*, 1993). As discussed in Chapter 1 a number of studies have confirmed a higher familial occurrence of cluster headache (Leone *et al.*, 2001; Montagna *et al.*, 1998; Russell *et al.*, 1995a) with some families exhibiting an autosomal dominant pattern of inheritance (D'Amico *et al.*, 1996; Montagna *et al.*, 1998; Russell *et al.*, 1995b; Spierings & Vincent, 1992).

Migraine and cluster headache together: The co-existence of cluster headache and migraine is less clear cut, although based purely on the prevalence of migraine one might expect at least 15% of cluster headache sufferers to have both (Steiner *et al.*, 1999). Our study found 26% of cluster headache sufferers gave a past history migraine consistent with IHS criteria (21% M, 40% F). The reported occurrence of migraine in patients with cluster headache has varied between 0 and 65% (Duvoisin *et al.*, 1961; Ekbom, 1974; Graham, 1972; Klapper *et al.*, 2000; Kudrow, 1980; Lance & Anthony, 1971; Manzoni *et al.*, 1983b; Sutherland & Eadie, 1972). Similar discrepancies exist with regard to the familial incidence of migraine in individuals with cluster headache. Our figure of 33% is higher than that of control populations. Some series have reported similar figures (Klapper *et al.*, 2000; Symonds, 1956), some higher (Dalsgaard-Nielsen, 1965; Kudrow, 1980) and others comparable to that in control populations (Ekbom, 1970a; Lance & Anthony, 1971). In addition, compared to control populations, the higher familial prevalence of cluster headache, the higher prevalence of migraine and

family history of migraine in cluster headache sufferers in this study suggest a genetic predisposition to primary head pain (Merikangas, 1996; Rasmussen *et al.*, 1991; Stewart *et al.*, 1992).

10.4.4 Natural History of Cluster Headache

Longitudinal data for cluster headache has been anecdotal. All the individuals in this study continue to suffer from cluster headache. The proportion of individuals continuing to suffer, addressed by decade of onset, tends to gradually decline whether the data is clinic-based (Manzoni *et al.*, 1981) or non clinic-based. Therefore unless there is either a true increase in incidence, or a bias of individuals with more recent onset cluster headache presenting for medical and support-group attention, it seems reasonable to assume that the natural history of the condition is to remit.

10.4.5 Diagnostic (in)accuracy

In a internet –based survey of 789 respondents (76% M) 87% qualified as having cluster headache according to IHS criteria (Klapper *et al.*, 2000). Similar findings to this study were reported. Diagnosis was delayed an average of 6.6 years from the onset of symptoms. The average number of physicians seen before the diagnosis was made was 4.3 and the average number of incorrect diagnoses 3.9. Four percent had unnecessary sinus or deviated septum surgery. Many inappropriate medications such as propranolol, amitriptyline, and antibiotics were prescribed while treatment with sumatriptan or oxygen was often denied due to failure to understand the nature of the disorder.

Particularly noteworthy in this study is the drastic reduction in mean time to diagnosis over the years. A neurologist diagnoses at least half of sufferers, and this proportion has

steadily increased with time. This may reflect better access to neurologists from primary healthcare; unfortunately there are currently no reliable statistics to validate this. Despite the reduction in mean time to diagnosis, the mean number of general practitioners seen prior to neurological referral has not changed and about two-thirds have already been seen by another specialist. Forty percent of those seen by a specialist other than a neurologist subsequently have an invasive procedure. This issue may be best addressed by targeting undergraduate medical training programs. This study has confirmed that the condition is quite stereotyped and there are few clinical differences between men and women. Diagnostic difficulties are most likely to arise from unfamiliarity with an uncommon syndrome, although an adequate history in most patients will match most textbook descriptions. Any doubt should trigger referral not invasive procedures.

10.4.6 Management Strategies in Cluster Headache

Acute attack treatments: The brevity of cluster headache attacks precludes most oral acute-relief treatments. Despite this and the availability of rapid abortive therapy with subcutaneous sumatriptan (Ekbom *et al.*, 1993; Ekbom & The Sumatriptan Cluster Headache Study Group, 1991; Ekbom *et al.*, 1992) more than half of the sufferers in this study had not been prescribed the parenteral preparation, while almost two-thirds had been prescribed the oral preparation for which there is no evidence base. The two main likely issues here are cost and concern regarding recurrent frequent use of the subcutaneous preparation. The ethical implications of cost are a particular problem. The cost of treatment must be balanced against withholding proven rapidly efficacious abortive treatment and contrasted with prescribing less efficacious cheaper treatments, or treatments which have no proven benefit.

Preventative treatment: Longer bouts, CCH and high attack frequency demand adequate prophylaxis. Our data show that while effective prophylactic options exist (see Chapter 4) sufferers are equally likely to be prescribed anti-migraine prophylaxis which has not been shown to be effective in the treatment of cluster headache (Table 10.9). Although a larger proportion of CCH sufferers had been prescribed verapamil, lithium, corticosteroids, or methysergide, there was no statistically significant difference in prescribed prophylactic treatment between ECH and CCH sufferers. Similarly there was no difference in prophylactic agents prescribed to women compared to men with the exception of a β -blocker. This may be due to the higher prevalence of migraine in women and general prescribing habits with regard to preventative treatment for headache. Notably a large proportion of sufferers continue to finance costly complementary therapies for which there is currently no evidence of benefit and provides re-emphasis on the importance of undergraduate and post-graduate education in regard to the management of cluster headache.

10.5 Summary

Cluster headache is a stereotyped primary pain syndrome characterised by strictly unilateral severe pain accompanied by ipsilateral autonomic features. The signature features of the syndrome are the circadian rhythmicity of the relatively short-lived daily/near daily attacks; and the periodicity of attack susceptible periods that are interspersed by periods of complete remission in the majority of individuals. The syndrome occurs about three times more commonly in men than women, and is clinically identical in both sexes. The mean time of onset occurs between the 3rd and 4th decade and ultimately the symptomatic periods are likely to remit. Although there are some shared clinical features, the syndrome of cluster headache is quite distinct from that of migraine, and this study recommends the addition of the feeling of agitation/lack

of exacerbation of headache, to the IHS diagnostic criteria. Epidemiological observations suggest that like migraine, the syndrome of cluster headache may occur in genetically predisposed individuals. The time to diagnosis of cluster headache has improved considerably over recent decades. This is most probably a result of better access to neurologists, who make the diagnosis over half of sufferers. However, there is a need to target both undergraduate and postgraduate training programs in order to reduce inappropriate investigation and treatment, and to optimise acute and prophylactic management strategies of this potentially treatable condition.

Table 10.1**Site of Pain**

%	Total	Males	Females	ECH	CCH
Retro-orbital	92	92	92	92	94
Temporal	70	70	71	68	81
Upper teeth	50	49	51	45*	67*
Forehead	46	48	40	45	42
Jaw	45	44	48	40*	65*
Cheek	45	44	46	40*	63*
Lower teeth	32	30	35	29	44
Neck	31	31	31	30	35
Nose	20	20	22	18	29
Ear	17	14*	26*	15*	27*
Shoulder	13	13	14	10*	25*
Vertex	7	7	6	5	8
Occiput	6	6	6	7	8
Parietal	1	0.5	3	2	0

* $p \leq 0.05$

Table 10.2
Side of Attacks

%	Total	Males	Females	ECH	CCH
Right-sided attacks	60	60	62	60	58
Left-sided attacks	38	38	37	37	42
Right and left equally	2	2	1	3	0
Side change within bout	18	19	15	14*	33*
Side change between bouts	18	18	18	18	-
Side change within and between bouts	3	3	2	3	-
Side change within attack	1	<1	<1	1	0

* $p \leq 0.05$

Table 10.3
Autonomic Features

%	Total	Males	Females	ECH	CCH
Lacrimation	91	92	88	92	88
Conjunctival injection	77	79	69	71	79
Nasal congestion	75	74	77	74	77
Ptosis / eye-lid swelling	74	72	78	73	79
Rhinorrhea	72	74	68	76*	56*

*p ≤ 0.05

Table 10.4
Additional Features

%	Total	Males	Females	ECH	CCH
Nausea	50	47	57	51	46
Vomiting	23	21	29	25	17
Photophobia	56	57	55	58	50
Phonophobia	43	45	37	41	52
Osmophobia	26	25	29	23*	38*
Restlessness †	93	94	92	93	94
Aura	14	13	18	14	15

* $p \leq 0.05$

† Restlessness or no exacerbation of pain with movement

Table 10.5**Periodicity of Attacks and Bouts, Alcohol triggering and Smoking History**

	Total	Males	Females	ECH	CCH
Bout duration (weeks)	8.6	8.9	7.8	-	
No. bouts/year	1	1	1.3	-	
Maximum no. attacks/24 hr	4.6	4.5	4.6	4.5	4
Maximum attack duration	159	166	141	166★	135★
Minimum attack duration	72	70	79	77	55
Seasonal propensity	43	45	40	-	-
Predictable time of onset of attacks-day	37	37	38	41	25
Predictable time of onset of attacks-night	73	74	71	74	71
Smoker	67	74*	49*	65	75
Ex-smoker	17	15	22	17	15
Alcohol trigger during bout	63	71*	42*	65	54
(Non-drinkers)	(16)	(10)*	(31)*	(14)	(25)

★Two patients described maximum attack duration for 129600 and 11520 minutes (90 and 8 days constantly in ECH and CCH respectively). These were therefore taken out of the analysis. Minimum attack duration fell within IHS guidelines. * $p \leq 0.05$

Table 10.6

**Male:Female (M:F) ratio, time to diagnosis and practitioners seen
relative to year of onset of cluster headache**

Time of Onset of cluster headache	Total (n)⌘	M:F Ratio	Mean time to diagnosis (years)	% Who had seen another specialist prior to diagnosis ⌘⌘	Mean number of general practitioners seen prior to diagnosis
Before 1950	1	1:0	12	100	3
1950-1959	6	2:1	22.3	100	3
1960-1969	21	2:1	17.2	81	6
1970-1979	46	2.1:1	9.5	67	2
1980-1989	89	3.5:1	6.4	62	3
1990-1999	66	2.3:1	2.6	70	2

⌘ Data missing on one patient

⌘⌘ Specialist other than a neurologist

Table 10.7

Specialists seen prior to diagnosis

Specialists seen prior to diagnosis	% M F	Treatment received	% M F
Dentist	45 45 46	Tooth extraction, splint, brace, filling, X-rays, maxillo-facial surgery	18 17 20
Ear, Nose, Throat Specialist	27 24 32	Sinus washout, surgery for nasal septum deviation, antibiotics, X-rays	13 14 11
Optician	32 34 26	Spectacle prescription altered, eye-exercises	3 2 3
Ophthalmologist	15 11* 23*	None	0
Other (physician, migraine clinic, neurosurgeon, psychiatrist, pain clinic)	7 6 11	None	0

* $p \leq 0.05$

Table 10.8
Acute Therapy

Acute Therapy	Total	Male	Female	ECH	CCH
Sumatriptan oral	61	57	71	49	65
Sumatriptan injection	45	45	45	45	46
Sumatriptan intranasal	14	15	12	13	19
Ergotamine derivative	56	53	66	59	48
Oxygen	37	37	38	36	42
Lignocaine intranasal	9	8	9	8	13
Other ☒	10	12	6	8	10

☒ Naratriptan, zolmitriptan, opiates, cannabis, benzodiazepines, capsaicin, ice

Table 10.9
Preventative Therapy

Prophylactic agent	Total	Male	Female	ECH	CCH
Verapamil	40	38	46	37	52
Corticosteroids	40	41	37	37	48
Lithium	40	38	45	37	50
Methysergide	37	35	40	34	48
Sodium Valproate	14	14	15	11	13
Beta-blocker	43	38*	54*	41	48
Pizotifen	32	28	33	30	38
Tricyclic antidepressants	32	33	32	29	31
Other ☒	10	10	13	9	17

☒ Carbamazepine, gabapentin, clonidine, other antidepressants, nerve block/surgical procedure (n=5), nifedipine, antihistamine, histamine desensitisation

* $p \leq 0.05$

Table 10.10**Alternative Therapy**

Alternative Therapy	Total	Male	Female	ECH	CCH
All treatments	63	61	69	64	58
Acupuncture	40	36	42	41	40
Herbal treatment	31	31	31	32	27
Chiropractic treatment	23	22	17	23	23
Homeopathy	18	18	19	19	15
Reflexology	10	8	14	8	17
Hypnosis	9	7	14	10	4
Spiritual therapy	9	8	11	7	15
Other ✕	7	8	6	7	8

✕ Massage, aromatherapy, relaxation therapy, physiotherapy, yoga

Figure 10.1: Distribution of bout frequency amongst the cohort of patients studied.

The distribution is unimodal with a mode bout frequency of 1 per year.

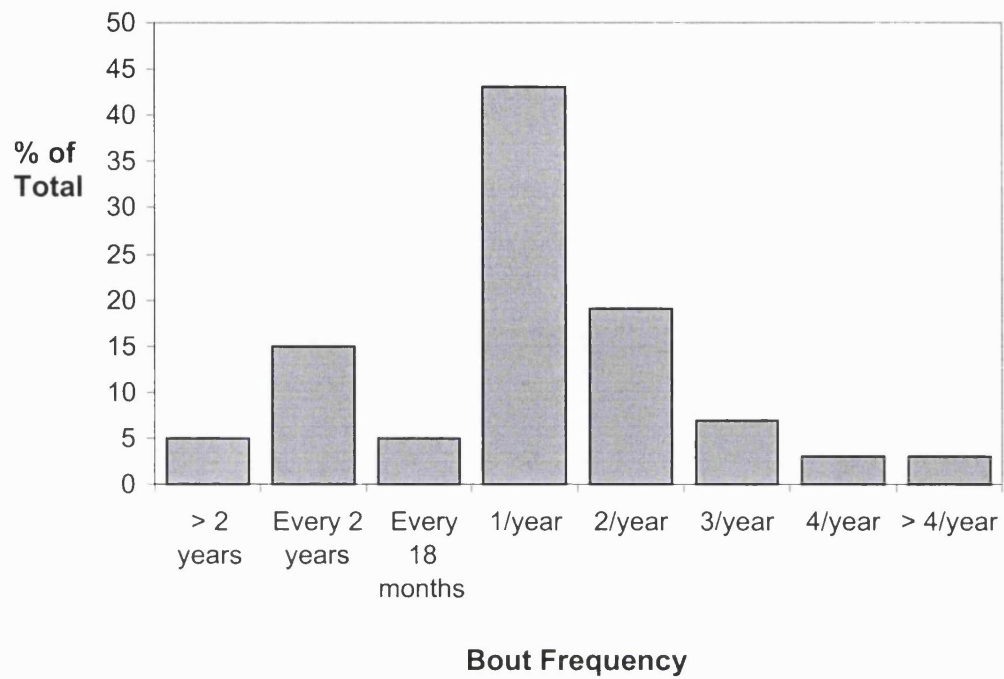


Figure 10.2: The distribution of the diagnosis of cluster headache made by neurologists by year in which the diagnosis was made. With the exception of the 1950-59 period in which the female number was too small to make any inference, the general trend is for a greater percentage of cluster headache patients to be diagnosed by neurologists. There is no apparent difference between males and females.

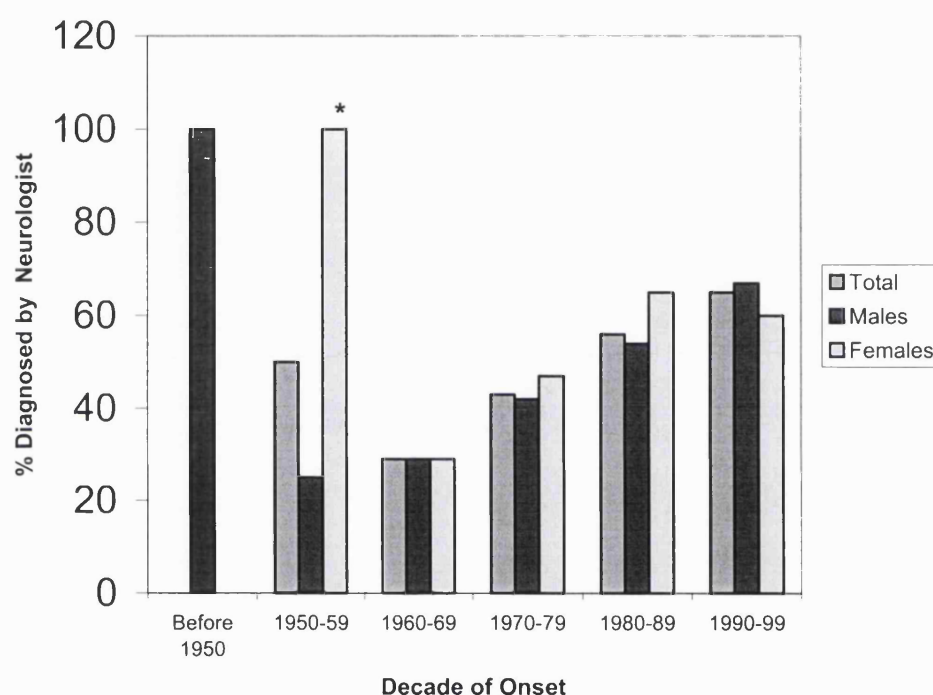
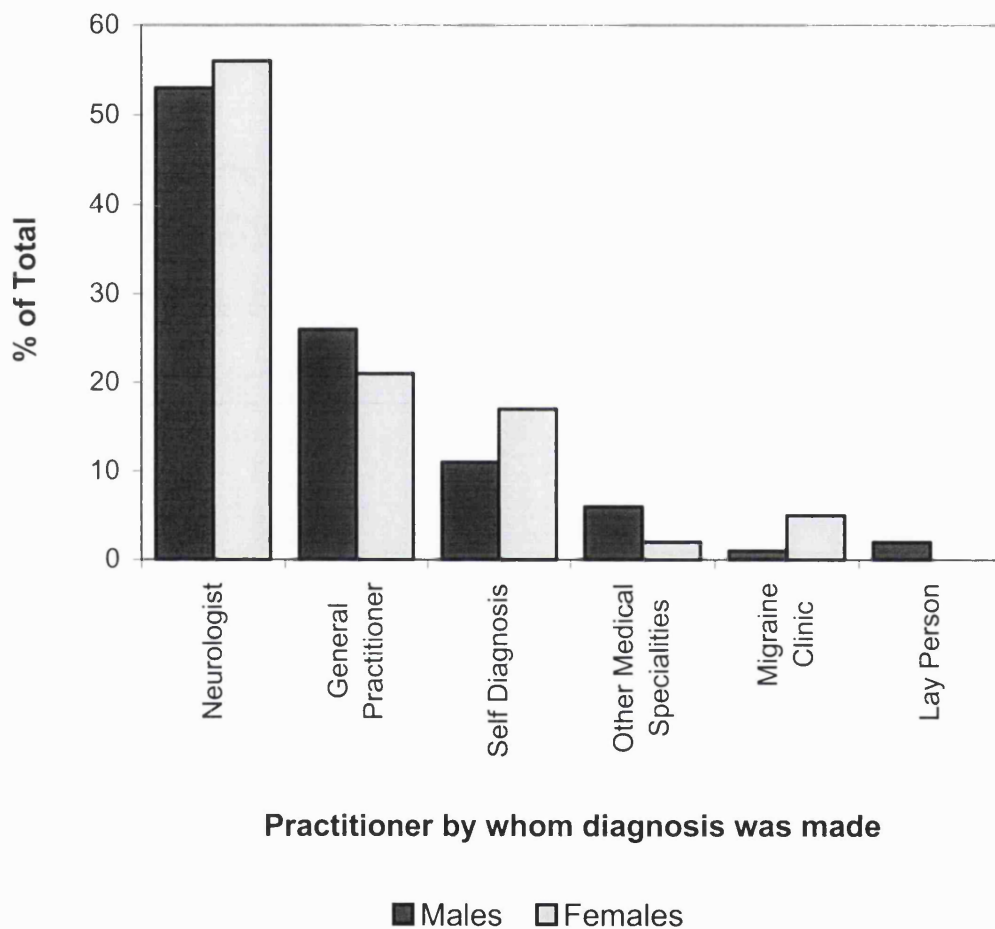


Figure 10.3: The distribution of diagnosed cluster headache amongst practitioners. About 50% of cluster headache sufferers had their diagnosis made by a neurologist and about 25% by a general practitioner. The combined self and lay person diagnosis is striking and may well continue with access to medical information over the internet.



PART 4

CONCLUSION

CHAPTER 11

Conclusion

Cluster headache has been described as early as the 17th century. The earliest reported description was in 1641 by the Dutch anatomist Nicolas Tulp of a gentleman with *"headache cured by Nature"*, where the patient *"lost a great amount of fluid from the nose ... (and) was relieved in a short period of time"*. He also describes the case of a merchant treated successfully with *"cupping"* on the occiput for *"squinting headache from which he suffered every spring.. . . in the beginning of the summer season, (the gentleman) was afflicted with a very severe headache, occurring and disappearing daily on fixed hours, with such an intensity that he often assured me that he could not bear the pain anymore or he would succumb shortly. For rarely it lasted longer than two hours. And the rest of the day there was no fever, nor indisposition of the urine, nor any infirmity of the pulse. But this recurring pain lasted until the fourteenth day ..."*. This description epitomises the stereotyped nature of the syndrome.

This thesis has examined a large group of mainly non-clinic based individuals with cluster headache. It provides one of the largest cohorts of individuals with cluster headache as defined by the 1988 classification criteria of the IHS. Moreover the study is prospective and each individual was interviewed by myself personally or by telephone. The study confirms the condition to be stereotyped and characterised by strictly unilateral predominantly first division trigeminal pain accompanied by ipsilateral autonomic features; the hallmark feature remains the remarkable periodicity associated with the acute attacks and bouts of attacks. The advantage of a prospective study is that a number of features that may not usually be associated with the syndrome can be investigated; it also allows the study of characteristics which have been mentioned anecdotally in previous reports. One of these is the characteristic of

movement which typically in migraine exacerbates the pain while in cluster headache patients tend to feel the need to move or movement notably does not exacerbate the pain. This is a criterion proposed for inclusion in the next revised classification criteria. Features which have been more commonly associated with migraine were also observed in cluster headache on direct questioning, such as nausea, vomiting, photophobia, phonophobia, osmophobia and aura symptoms. The photophobia is eluded to in Tulp's description given above. There are some who would propose inclusion of these criteria to the IHS classification for cluster headache. But the essence of such studies is to differentiate the features which are shared and specific to each syndrome. Only then can we obtain patient homology with which to adequately address therapeutics and pathophysiology as exemplified in the PET studies detailed in this thesis.

Poor diagnostic accuracy and management of the syndrome is no doubt due to the rarity of the condition, a factor further compounded by the episodicity, such that most general practitioners may encounter only one or two individuals with cluster headache throughout their life-time of clinical practice. However there are two points to make from this. First, and most obvious, the syndrome is probably the most excruciating pain syndrome known to man and adequate management can revolutionise the quality of life in such patients. Secondly, despite its rarity the homogeneity of this patient group provides the ideal opportunity to study pathophysiological mechanisms in primary head pain, which can hence be used to further our understanding of the more common primary head pain syndromes which beset a large proportion of neurology outpatient clinics and the general population.

The PET studies in part 2 of this thesis identified activation of the posterior hypothalamus during the acute cluster headache attack in patients with CCH. The study

has been pursued outside the scope of this thesis to address the activation pattern in patients with ECH also. Activation of the hypothalamus is not a region which has been consistently reported in previous PET studies of pain. In the context of the characteristic clinical features and neuroendocrine abnormalities in cluster headache, suggestive of a disturbance of the hypothalamus, it seems reasonable to conclude that the observed PET activation is specific to the syndrome. The third PET study was performed during an acute migraine headache attack. Dorsorostral brainstem activation was observed but no hypothalamic activation. While a single PET study cannot exclude that there may also be activation of the hypothalamus if a larger group of patients were imaged, the chance of imaging a number of patients with migraine during an active cluster bout is going to be far less likely than what appears to be the relatively straightforward but in fact practically very difficult task of repeating the study by Weiller and colleagues. This is the first study to reproduce the findings of brainstem activation in migraine headache since that published by Weiller and colleagues. Activation was also observed in the region of the cranial vessels and was strongly correlated to the pain. It is unfortunate that the temporal resolution of oxygen-15 tracer PET studies does not allow visualisation of whether the neural changes are preceded or followed by the vascular changes. However, the same changes are observed during spontaneous cluster headache, triggered migraine headache and secondary first division trigeminal pain suggesting that vascular activation is a secondary phenomenon to activation of first division trigeminal nociception. The ultimate goal for any disease ideally is cure, realistically is the availability of efficacious and safe therapeutic agents. The prime importance of central mechanisms in primary head pain, as supported by this thesis, has gradually evolved over the last two decades. This is exemplified by the advent of the 'triptans' and address of factors such as drug lipophilicity to target central mechanisms involved in pain.

In conclusion this thesis has shown that cluster headache is a head pain syndrome characterised by strictly unilateral first division trigeminal head pain, ipsilateral autonomic features and a circadian periodicity to the short lived attacks and bouts of attacks. The syndrome is more common in women than previously reported. There continue to be diagnostic delays and the majority of patients are diagnosed by a neurologist. Increasing access to a neurologist may account for the observed improvement in time to diagnosis observed over the last five decades. Despite this most individuals are not adequately treated. Education at both undergraduate and postgraduate levels may best address these two problems. Individuals with cluster headache provide a patient group with distinct symptoms with which to investigate pathophysiological mechanisms in primary head pain. The functional imaging studies in this thesis support that cluster headache and migraine are essentially disorders of the central nervous system and each is associated with a specific brain activation pattern. Activation of the cranial vessels appears to be a shared phenomenon which most likely is secondary to activation of first division trigeminal nociception. Thus the term neurovascular headache is a more appropriate term to describe the primary pain syndromes of migraine and cluster headache.

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