

A population-based study of familial hemiplegic migraine suggests revised diagnostic criteria

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Summary

Familial hemiplegic migraine (FHM) is a rare autosomal dominantly inherited subtype of migraine with aura. The clinical characteristics of FHM have been described previously in selected materials or case studies, but population-based studies are important in order to analyse the full spectrum of the disorder. The aim of the present study was to perform a systematic search for familial cases of migraine with an aura that included motor weakness in order to generate non-selected material of as many FHM cases as possible in the Danish population of 5.2 million inhabitants, and to compare this material with already available population-based clinical descriptions of migraine with typical aura (MA). Due to the rarity of FHM, traditional population-based methods were not feasible. Therefore, the search strategy employed a computer search of the National Patient Register, screening >27 000 case records from headache clinics and private neurologists, and advertisements. A total of 147 affected FHM patients from 44 families were identified. FHM patients most often had all four 'typical' aura symptoms (visual, sensory, aphasic and motor

symptoms) and all had at least two of these aura symptoms during FHM attacks. The motor, sensory and visual aura symptoms were all similar in type to the motor, sensory and visual aura symptoms in MA, but FHM had a statistically significantly longer duration of the visual and sensory aura symptoms, and these and other aura symptoms often fulfilled the criteria of the International Headache Society for prolonged aura. In addition, 69% had basilar migraine (BM) symptoms during FHM attacks. The order of the aura symptoms was usually visual, followed by sensory, aphasic, motor and, lastly, basilar-type migraine symptoms. Headache was present in 99% of FHM patients during FHM attacks, whereas the aura symptoms more often occurred without headache in MA. Headache duration was significantly longer in FHM compared with MA. Based on these data, we suggest more precise diagnostic criteria for FHM and a more clear clinical distinction between FHM and BM. Our results have significant implications for case finding in genetic studies and for clinical migraine differential diagnosis.

Keywords: familial hemiplegic migraine; population-based; clinical characteristics; diagnostic criteria

Abbreviations: BM = basilar migraine; FHM = familial hemiplegic migraine; IHS = International Headache Society; MA = migraine with typical aura; MO = migraine without aura

Introduction

Familial hemiplegic migraine (FHM) is a rare autosomal dominantly inherited subtype of migraine with aura, where attacks are associated with some degree of motor weakness (Headache Classification Committee of the International Headache Society, 1988). The interest in FHM has greatly increased following the demonstration of linkage to chromosome 19p13 (Joutel *et al.*, 1993) and the subsequent identification of several causative missense mutations in the *CACNA1A* gene on this chromosome (Ophoff *et al.*, 1996), that account for ~50% of FHM families (Ducros *et al.*, 2001).

The rarity of FHM explains why available clinical data are based on selected families (Clarke, 1910; Whitty, 1953; Blau and Whitty, 1955; Rosenbaum, 1960; Bradshaw and Parsons, 1965; Ohta *et al.*, 1967; Young *et al.*, 1970; Heyck, 1973; Glista *et al.*, 1975; Parrish and Stevens, 1977; Zifkin *et al.*, 1980; Jensen *et al.*, 1981; O'Hare *et al.*, 1981; Haan *et al.*, 1994, 1995; Rajput and Kramer, 1995; Ahmed *et al.*, 1996; Terwindt *et al.*, 1996, 1998b; Kramer *et al.*, 1997; Hayashi *et al.*, 1998; Echenne *et al.*, 1999; Ducros *et al.*, 2000, 2001) and probably why population-based surveys have not been

available. The aim of the present study was to perform a population-based analysis of the migraine aura and headache characteristics of FHM and compare these characteristics with those found in a previous Danish population-based study of migraine with typical aura (MA) (Russell and Olesen, 1996).

Material and methods

Data collection

A systematic search was performed employing three different search strategies in the Danish population of 5.2 million inhabitants. The search included a computer search of the National Patients Register, screening >27 000 case records from headache clinics and private neurologists and advertisements for hemiplegic migraine patients. All probands (the first affected patient identified in a family) with FHM from this study population were included. Probands and relatives were interviewed and diagnosed using a semi-structured validated telephone interview according to the diagnostic criteria of the International Headache Society (IHS; Headache Classification Committee of the International Headache Society, 1988), except that, in order to analyse FHM and MA separately, probands and relatives who were diagnosed with MA had to have attacks of migraine with aura which did not include motor weakness.

All first-degree relatives >15 years of age were interviewed, whereas first-degree relatives of ≤ 15 years were only contacted for a telephone interview if they were suspected of having or previously having had headache and/or aura symptoms. Among second- and third-degree or more distant relatives, as many relatives as could be traced in the families were contacted for a telephone interview, except children/young people living with their parents not suspected of having or having had headache or aura symptoms, as well as a few adult relatives not suspected by history of having had headache or aura symptoms. One neurological research fellow experienced in headache diagnostics conducted all the telephone interviews and physical and neurological examinations of FHM-affected patients. Furthermore descriptions of CT and/or MRI scans of the cerebrum were collected on affected patients who reported previously having had a CT and/or MRI scan. If a patient had had both scans, only the MRI scan was counted.

A total of 2866 [1914 recruited patients, 952 relatives (976M : 1890F)] were available. Two hundred and four patients were non-contactable. Those interviewed by telephone were labelled participants (1915 patients) and those not interviewed were labelled non-participants (411 patients). The participation rate among recruited patients was 79% (1446 out of 1828). The participation rate among relatives was 94% (469 out of 498). Further details about material, non-participants, criteria for motor aura and representativeness have been reported elsewhere (L. L. Thomsen *et al.*, 2002, in press).

The project was approved by the Danish ethical committees.

Definition of familial hemiplegic migraine

Families with FHM according to the criteria of the IHS (Headache Classification Committee of the International Headache Society, 1988) were included in the study.

Definition of 'possibly affected' FHM relatives

Patients who had only had one FHM attack, and thus did not fulfil the criteria for FHM, or patients who by history had or had had FHM, but where the diagnosis could not be verified with certainty, were classified as 'possibly affected'.

Definition of basilar-type symptoms and basilar migraine (BM)

'Basilar-type symptoms' were defined as simultaneous bilateral paresis and/or paresthesiae, simultaneous visual symptoms in both the temporal and nasal fields of both eyes, dysarthria, vertigo, diplopia, tinnitus, decreased hearing, decreased level of consciousness, loss of balance when walking, drop attacks (defined as a sudden fall at the beginning of a migraine attack due to loss of postural control without loss of consciousness and with complete recovery in seconds), crossed symptoms (cranial nerve symptoms contralateral to symptoms in the extremities) and symptoms switching from one side of the body to the other during the attack. The questions were based on the IHS criteria for BM (Headache Classification Committee of the International Headache Society, 1988).

Basilar migraine was confirmed in patients having at least two of the following symptoms: simultaneous bilateral paresis and/or paraesthesiae, simultaneous visual symptoms in both the temporal and nasal fields of both eyes, dysarthria, vertigo, double vision, tinnitus, decreased hearing or decreased level of consciousness. Loss of balance when walking is not necessarily ataxia, and the presence of loss of balance was therefore not used to diagnose BM. The permanent ataxia present in two families was unrelated to attacks, and was therefore not counted. The questions about drop attacks, crossed symptoms and symptoms switching from one side to the other are not part of the IHS criteria of BM and therefore were not used to diagnose BM.

Data processing and statistical analysis

All data were processed and statistical analyses were performed using SPSS Base System 10.0 for Windows 98. The χ^2 test, Mann-Whitney test, Kruskal-Wallis test, *t* test for independent samples and 95% confidence intervals (CIs) were used as appropriate depending on the type of data. A 0.05 level of significance was used in single tests. When

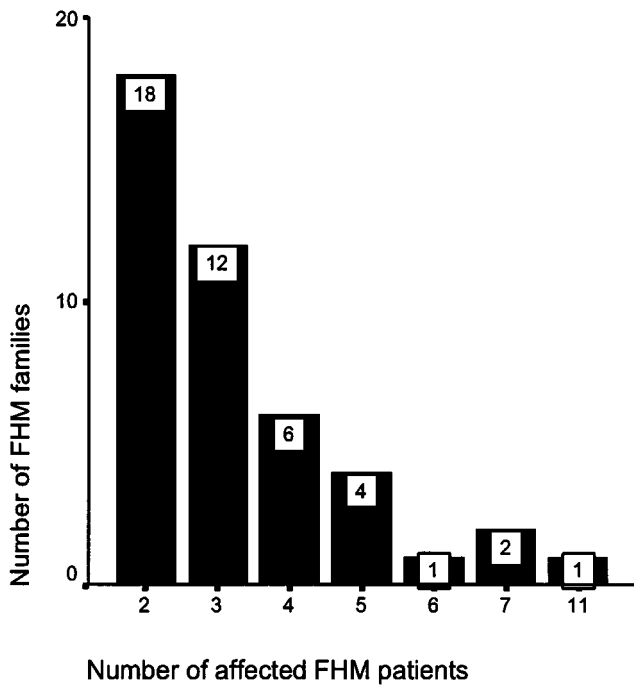


Fig. 1 The distribution of affected patients in familial hemiplegic migraine families.

testing for multiple symptoms, a 0.001 level of significance was chosen in order to compensate for mass significance.

Results

A total of 147 subjects affected from 44 Danish FHM families were identified. The 44 (9M : 35F) probands had 103 (33M : 70F) affected and 22 (13M : 9F) possibly affected relatives among 952 (450M : 502F) relatives, consisting of 240 first-degree relatives, 264 second-degree relatives and 448 third-degree or more distant relatives. The status ‘possibly affected’ was assigned to (i) patients having only one hemiplegic migraine attack ($n = 6$); and (ii) patients having a history of hemiplegic attacks ($n = 16$). Of the latter, 10 were dead; one patient was impossible to understand due to ataxic speech; one patient had dementia; and two patients refused to participate for unspecified reasons. Furthermore two children were unable to describe their attacks properly. The possibly affected patients were not included in this study.

Number of affecteds per family

The number of affected individuals per FHM family is illustrated in Fig. 1.

Mode of inheritance

An autosomal dominant mode of inheritance seemed to be present in 77% (34 out of 44) of our FHM families, of which

Table 1 Results of the physical and neurological examination of familial hemiplegic migraine (FHM) patients ($n = 143$)*

	%	<i>n</i>
Normal physical and neurological examination	85	121
Cerebellar ataxia (no other neurological deficits)	7	10
Symptoms caused by previous stroke (FHM since childhood, stroke in their fifties)	2	3
Minor neurological deficits (i.e. isolated sensory disturbances or reduced coordination by a limb)	5	7
Sensory ataxia (verified by nerve conduction investigation)	<1	1
Post-operative symptoms caused by previous surgery for cerebral aneurysm	<1	1

*Four affecteds were not examined, i.e. three did not want to participate and one had emigrated.

some families seem to have reduced penetrance, whereas a complex mode of inheritance was likely in 23% (10 out of 44).

Age

The mean age among affecteds was 37 years (95% CI: 35–40; range 9–82 years). The mean age at onset was 17 years (95% CI: 15–18; range 1–45 years). There was no statistically significant difference in mean age at onset between gender ($P = 0.843$, *t* test) or between small and large FHM families ($P = 0.803$, *t* test). In affecteds, but without attacks in the last 2 years ($n = 39$), the mean age at the last attack was not statistically significantly different in males compared with females or in small compared with large FHM families, i.e. 35 years (95% CI: 26–45) in males and 35 years (95% CI: 30–41) in females, and 38 years (95% CI: 29–47) in small and 34 years (95% CI: 29–39) in large FHM families.

Physical and neurological examination

The results of the clinical and neurological examination of FHM patients are shown in Table 1. Four FHM patients were not examined due to refusal to participate for unspecified reasons ($n = 3$) and emigration ($n = 1$).

Head traumas as FHM trigger

Nine per cent (13 out of 147) reported minor head traumas as a trigger factor of FHM attacks.

Attack frequencies

The distribution of lifetime number of FHM attacks by gender is shown in Table 2. There was no significant difference between gender in lifetime number of FHM attacks ($P = 0.678$, Kruskal–Wallis test). Patients aged >50 years had a lower number of attacks during the last year compared with patients aged ≤50 years. Thus, in the age group >50 years, 68%

Table 2 The distribution of lifetime number of familial hemiplegic migraine attacks by gender

Lifetime number of attacks	Males (n = 42)		Females (n = 105)		Overall (n = 147)	
	%	n	%	n	%	n
2-4	12	5	17	18	16	23
5-9	9	4	4	4	5	8
10-49	24	10	24	25	24	35
50-99	24	10	15	16	18	26
>100	31	13	40	42	37	55

(19 out of 28) had not had attacks during the last year compared with 32% (38 out of 118) in the age group of ≤50 years ($P = 0.001$, Fisher's exact test). The majority (73%, 32M : 76F) had had attacks within the last 2 years, and of the 27% (10M : 29F) that had not had attacks within the last 2 years, 87% no longer had attacks after the age of 50 years.

Aura symptoms

In FHM, motor aura symptoms are obligatory. The most common other aura symptoms were sensory aura (98%), visual aura (89%) and aphasia (72%). Furthermore, 69% had co-occurrence of BM, with basilar-type symptoms during FHM attacks. The distribution of the various combinations of aura symptoms during FHM attacks is illustrated in Fig. 2.

The four aura symptoms (motor, sensory, visual and aphasic) frequently were all present during an attack ($n = 95$) and, if not, a combination of three aura symptoms was nearly always experienced during FHM attacks ($n = 44$). Very rarely, motor aura symptoms were combined only with sensory or visual aura symptoms ($n = 8$) and never exclusively with aphasia. Table 3 shows the lifetime occurrence of the aura symptoms during FHM attacks.

Of the 95 patients with all four aura symptoms as part of their hemiplegic attacks, 93% always had sensory aura, 81% always had visual aura and 64% always had aphasic symptoms during their attacks. Furthermore, 52% of these patients always had basilar-type symptoms present during attacks.

In 49% of the patients, all four aura symptoms and at least two BM symptoms were present. Of these patients, 83% reported that aura symptoms occurred one at a time, one succeeding the other. The rest of the patients were uncertain and preferred not to answer the question. The most frequent temporal orders of succession of the aura symptoms were visual, sensory, motor, aphasic and basilar-type (73%), followed by sensory, motor, visual, aphasic and basilar-type (8%), sensory, visual, motor, aphasic and basilar-type (3%), visual, aphasic, sensory, motor and basilar-type (2%) or aphasic, visual, sensory, motor and basilar-type (2%). In 12%, aura successions other than the above were reported.

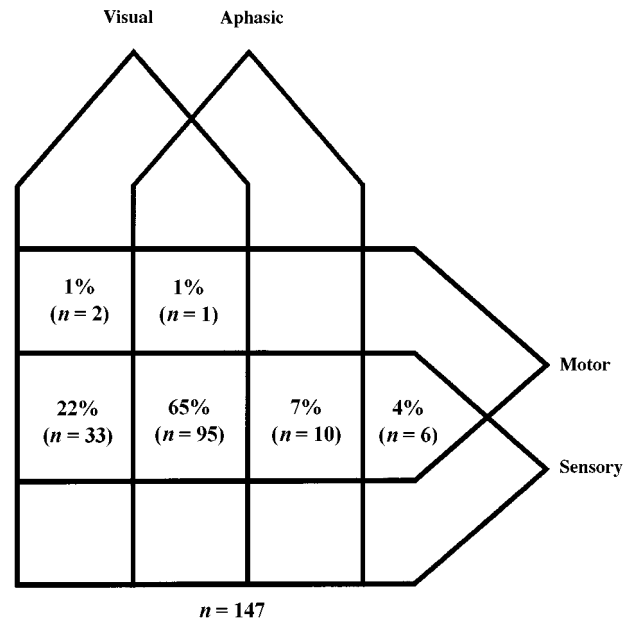


Fig. 2 Venn diagram illustrating the distribution of the various aura symptoms during familial hemiplegic migraine attacks.

However, several patients reported that the succession of the aura symptoms could vary from attack to attack.

There was no significant difference in the mean duration of the aura symptoms in patients with four aura symptoms ($n = 95$) compared with patients with three aura symptoms ($n = 44$) ($P > 0.05$, t test) nor in FHM patients from large FHM families (≥ 4 affected) compared with FHM patients from small FHM families (< 4 affected) ($P = 0.507$ motor aura; $P = 0.423$ sensory aura; $P = 0.178$ visual aura; and $P = 0.017$ aphasic aura symptoms; t test). Furthermore, we did not find any significant differences in aura symptoms or headache characteristics in FHM patients from large compared with small FHM families ($P > 0.001$, χ^2 test).

Motor aura symptoms

The characteristics of the FHM aura symptoms are shown in Table 4.

Motor aura symptoms are obligatory during FHM attacks. Fifty-nine per cent (87 out of 147) of the FHM patients had hemiparetic distribution of the motor aura symptoms (in both the upper and lower extremity on the same side), whereas 41% (60 out of 147) had a non-hemiparetic distribution of the motor aura symptoms during FHM attacks. Sixty-six per cent (29 out of 44) of FHM families comprised affected patients that were either affected in an arm and a leg or affected in an arm or a leg. Twenty per cent (nine out of 44) of FHM families were comprised exclusively of patients with auras affecting an arm and a leg and 14% (six out of 44) were comprised exclusively of patients affected in an arm or a leg.

The majority 98% (144 out of 147) experienced motor aura symptoms in association with sensory aura symptoms,

Table 3 Lifetime occurrence of aura symptoms during familial hemiplegic migraine attacks

Percentage of lifetime attacks	Motor (n = 147)*		Sensory (n = 135)*		Visual (n = 129)*		Aphasic (n = 106)*		BM (n = 80)*	
	%	n	%	n	%	n	%	n	%	n
1-24	0	0	1	1	2	2	4	4	15	12
25-49	0	0	1	1	2	3	4	4	6	5
50-74	0	0	0	0	7	9	7	8	6	5
75-99	0	0	1	2	6	8	1	1	5	4
100	100	147	97	131	83	107	84	89	68	54

*n = number of patients answering the specific question.

Table 4 Characteristics of the familial hemiplegic migraine aura symptoms

	Motor aura (n = 147)		Sensory aura (n = 144)		Visual aura (n = 131)		Aphasia (n = 106)	
	%	n	%	n	%	n	%	n
Unilateral	100	147	100	144	61	80	-	-
Gradual progression	97	143	99	142	92	121	-	-
Localization								
Face	51	75	85	122	-	-	-	-
Tongue	57	83	83	119	-	-	-	-
Hand	98	144	99	143	-	-	-	-
Arm	93	137	95	137	-	-	-	-
Foot	59	87	68	98	-	-	-	-
Leg	59	86	67	97	-	-	-	-
Body	30	43	35	50	-	-	-	-
Duration of gradual progression (motor n = 134/sensory n = 137/visual n = 122)								
<1 min	4	6	2	3	8	10	-	-
1-4 min	7	9	7	9	8	10	-	-
5-30 min	75	101	72	99	75	91	-	-
31-60 min	10	14	13	18	7	9	-	-
61-90 min	0	0	1	1	0	0	-	-
91-120 min	2	2	2	3	0	0	-	-
>120 min	2	2	3	4	2	2	-	-
Duration (motor n = 146/sensory n = 144/visual n = 130/aphasia n = 106)								
<1 min	0	0	0	0	0	0	0	0
1-4 min	0	0	0	0	1.5	2	0	0
5-60 min	42	61	47	67	72	94	41.5	44
61-120 min	25	37	26	38	16	20	14	15
121-720 min	19	27	19	28	9	12	37	39
721-1440 min	12	18	7	10	1.5	2	7.5	8
>1440 min	2	3	1	1	0	0	0	0
Starts in the centre of the visual field (n = 124)	-	-	-	-	23	29	-	-
Starts in periphery of the visual field (n = 124)	-	-	-	-	49	61	-	-
Scotoma	-	-	-	-	79	103	-	-
Preserved central vision	-	-	-	-	3	4	-	-
Zig-zag lines (fortification)	-	-	-	-	50	66	-	-
Flickering light	-	-	-	-	89	117	-	-
Problems articulating speech	-	-	-	-	-	-	92	97
Problems finding the right words	-	-	-	-	-	-	66	70
Problems in understanding what other people say	-	-	-	-	-	-	10	10
Problems in the production of language	-	-	-	-	-	-	96	101

and in these patients the motor aura symptoms affected only those parts of the body also affected by sensory aura symptoms.

Mean gradual progression time of the motor aura symptoms was 27 min (95% CI: 15-38 min). The mean duration of the motor aura symptoms was 5 h 36 min (95% CI: 242-429

min). Fifty-eight per cent (85 out of 146) had a prolonged duration (>60 min) of the motor aura symptoms, but the majority (98%, 143 out of 146) had an aura duration that was <24 h.

Fifty-nine per cent of the patients reported that the hemiparesis affected the extremities on the same side in every attack; the right side was affected in 60% and the left side in 40% ($P = 0.107$, χ^2 test). Forty-one per cent of FHM patients experienced a side shift of sensory and/or motor symptoms from attack to attack, and 8% occasionally had simultaneous bilateral sensory or motor aura symptoms from the onset of attack.

Sensory aura symptoms

The characteristics of the sensory aura symptoms are shown in Table 4.

The gradual progression frequently was within 60 min (94%, 129 out of 137) and the duration for the majority was <12 h (92%, 133 out of 144) and very seldom >1 day (1%, one out of 144). The mean gradual progression time of the sensory aura symptoms was 32 min (95% CI: 20–45 min) and the mean duration was 3 h 43 min (95% CI: 156–291 min). Fifty-three per cent (77 out of 144) had prolonged duration of the sensory aura symptoms (>60 min).

Visual aura symptoms

The characteristics of the visual aura symptoms are shown in Table 4.

The mean gradual progression time of the visual aura symptoms was 16 min (95% CI: 12–21 min). The mean duration of the visual aura symptoms was 1 h 40 min (95% CI: 64–137 min). Twenty-six per cent (34 out of 130) had a prolonged duration (>60 min) of the visual aura symptoms.

Of other visual symptoms not included in the semi-structured telephone interview, homonymous hemianopsia with a negative visual image and without fortification lines was reported in five patients.

Aphasic symptoms or other speech disturbances

The characteristics of the speech disturbances are shown in Table 4.

Only those with problems in the production of language (not due to dysarthria) and problems in understanding what other people say (not due to pain) were included as having aphasia. Eight individuals had dysarthria but no aphasia. The mean duration of the aphasia was 3 h 7 min (95% CI: 119–256 min). Fifty-eight per cent (62 out of 106) had prolonged (>60 min) duration of the aphasic aura symptoms.

Basilar migraine symptoms

One hundred and one patients fulfilled the IHS criteria for FHM and for BM; the characteristics of the basilar-type

Table 5 Basilar-type symptoms experienced by 101* of 147 patients with familial hemiplegic migraine

	%	n
Definite brainstem symptoms		
Diplopia	51	52
Decreased hearing	48	48
Crossed symptoms	1	1
Bi-cortical and/or brainstem symptoms		
Dysarthria	73	74
Loss of balance	72	73
Vertigo	72	73
Bilateral visual symptoms	53	54
Switching from one side to the other	34	34
Decreased level of consciousness	31	31
Tinnitus	29	29
Drop attacks	22	22
Bilateral paresis and/or paresthesia	11	11

*Number of FHM patients fulfilling IHS criteria for basilar migraine.

symptoms experienced by these patients are illustrated in Table 5.

Sixty-eight per cent of these patients fulfilled BM criteria during all FHM attacks.

In 39% (17 out of 44) of FHM families, all FHM affecteds fulfilled the IHS criteria for BM during FHM attacks. In 11% (five out of 44) of FHM families, none of the FHM affecteds fulfilled the IHS criteria for BM during FHM attacks.

Acute onset aura

According to the IHS classification, acute onset aura is defined as migraine with aura developing fully in <5 min. Fifteen patients had exclusively acute onset motor aura symptoms, 12 patients had acute onset sensory aura symptoms and 20 patients had acute onset visual aura symptoms. Of the 10% (15 out of 147) of patients with acute onset motor aura symptoms, 73% (11 out of 15) reported that the motor aura symptoms gradually progressed in <5 min. Of the 8% (12 out of 144) of patients with acute onset sensory aura symptoms, 83% (10 out of 12) reported that the sensory aura symptoms gradually progressed in <5 min. Of the 15% (20 out of 131) of patients with acute onset visual aura symptoms, 50% (10 out of 20) reported that the visual aura symptoms gradually progressed in <5 min. In patients with acute onset of aura symptoms, the aura symptoms occurred in sequence, had a typical duration or were followed by a typical headache phase, indicating the migrainous nature of the symptoms.

Headache phase

The characteristics of the headache phase during FHM attacks are shown in Table 6.

During FHM attacks, 95% of the patients always experienced a headache, 4% experienced a headache in some attacks and 1% never experienced headache.

Table 6 Characteristics of headache phase (non-treated or insufficiently treated) during familial hemiplegic migraine attacks

	Males (n = 41)		Females (n = 104)		Overall (n = 145)*	
	%	n	%	n	%	n
Pain characteristics						
Location						
Unilateral	46	19	56	58	53	77
Bilateral	54	22	44	46	47	68
Character (n = 144)						
Pulsating	80	33	82	84	81	117
Pressing/tightening	20	8	18	19	19	27
Intensity						
Mild	2	1	5	5	4	6
Moderate/severe	98	40	95	99	96	139
Aggravation by routine physical activity	95	39	97	101	97	140
Duration						
<30 min	0	0	0	0	0	0
30–240 min	5	2	8	8	7	10
241–1440 min	68	28	63	66	65	94
1441–4320 min	22	9	28	29	26	38
>4320 min	5	2	1	1	2	3
Accompanying symptoms						
Nausea	88	36	83	86	84	122
Vomiting	59	24	62	64	61	88
Photophobia	85	35	88	91	87	126
Phonophobia	80	33	88	91	86	124

*Two affecteds did not have headache during FHM attacks.

No significant difference was found between gender regarding pain characteristics or accompanying symptoms ($P > 0.05$, χ^2 test or Fisher's exact test).

Succession of visual aura symptoms and headache

Headache followed the visual aura symptoms in 73%, came before the visual aura symptoms in 17%, while both occurred simultaneously in 10%.

Comparison between FHM and MA

The results of the 147 FHM patients were compared with the aura and headache characteristics of 163 patients with MA collected in a previous Danish population-based study using almost the same validated telephone interview (Russell and Olesen, 1996).

Lifetime numbers of attacks were not significantly different in FHM compared with MA ($P = 0.083$, Kruskal–Wallis test).

The symptom composition and the order of symptoms were rather similar to those of MA, but the visual aura symptoms more often started peripherally ($P < 0.001$, Fisher's exact test), caused a scotoma ($P < 0.001$, Fisher's exact test) and obscured the central vision ($P < 0.001$, Fisher's exact test) in FHM as compared with MA. Sensory aura symptoms more

often involved the leg ($P < 0.001$, Fisher's exact test) or foot ($P < 0.001$, Fisher's exact test). No significant differences were found in the distribution of the motor aura symptoms. Dysarthria was significantly more frequent ($P < 0.001$, Fisher's exact test).

In MA, the visual aura symptoms were more often shaped like zig-zag lines compared with FHM ($P < 0.001$, Fisher's exact test).

Other major differences were that speech disturbances were present in 72% (95% CI: 65–79%) in FHM compared with 18% (95% CI: 12–24%) in MA, sensory aura symptoms were present in 98% (95% CI: 96–100%) in FHM compared with 31% (95% CI: 24–38%) in MA, motor aura symptoms were present in 100% in FHM compared with 6% (95% CI: 3–9%) in MA, and visual aura symptoms were present in 89% (95% CI: 84–94%) in FHM compared with 99% (95% CI: 97–100%) in MA.

Thus, in FHM, all four aura symptoms or a combination of three or at least two aura symptoms were always present during attacks.

The gradual progression time and the duration of aura symptoms during FHM and MA attacks are shown in Table 7. There was no significant difference in the gradual progression time of the aura symptoms in FHM compared with MA ($P > 0.001$, Kruskal–Wallis test). However, the duration of each symptom often was prolonged (>60 min) (58% motor aura, 53% sensory aura, 26% visual aura and 58% aphasic

Table 7 Gradual progression and duration of aura symptoms in familial hemiplegic migraine (FHM) and migraine with typical aura (MA)

	FHM		MA	
	%	n	%	n
Motor aura symptoms				
Gradual progression time^a				
<5 min	10	15	0	0
5–30 min	69	101	63	5
31–60 min	10	14	13	1
>60 min	12	17	25	2
Duration^b				
<5 min	0	0	0	0
5–30 min	21	31	33	3
31–60 min	20	30	0	0
>60 min	59	86	67	6
Sensory aura symptoms				
Gradual progression time^c				
<5 min	8	12	2	1
5–30 min	69	99	82	41
31–60 min	13	18	2	1
>60 min	10	15	14	7
Duration^d				
<5 min	0	0	2	1
5–30 min	22	31	67	34
31–60 min	25	36	12	6
>60 min	54	77	20	10
Visual aura symptoms				
Gradual progression time^e				
<5 min	15	20	0	0
5–30 min	70	91	85	132
31–60 min	7	9	11	17
>60 min	8	11	5	7
Duration^f				
<5 min	2	2	0	0
5–30 min	46	60	71	111
31–60 min	26	34	21	32
>60 min	27	35	8	13
Aphasic aura symptoms				
Duration^g				
<5 min	22	33	0	0
5–30 min	29	43	59	17
31–60 min	12	18	24	7
>60 min	36	53	17	5

^a $P = 0.39$; ^b $P = 0.147$; ^c $P = 0.868$; ^d $P < 0.001$; ^e $P = 0.015$;

^f $P < 0.001$; ^g $P = 0.005$ by Kruskal–Wallis test.

aura symptoms) during FHM attacks, with a statistically significant longer duration of the visual and sensory aura symptoms compared with MA attacks ($P < 0.001$; Kruskal–Wallis test).

The headache duration was significantly increased in FHM compared with MA ($P < 0.001$, Kruskal–Wallis test; and $P < 0.001$, χ^2 test) but there were no statistically significant differences in either pain characteristics or accompanying symptoms ($P = 0.249$ unilateral/bilateral location, $P = 0.564$ pulsating/pressing character, $P = 0.431$ moderate/severe intensity, $P = 0.002$ aggravation by routine physical activity,

$P = 0.116$ nausea, $P = 0.001$ vomiting, $P = 0.836$ photophobia and $P = 0.004$ phonophobia, Kruskal–Wallis test).

Co-occurrence of other migraine forms

Sixty-five per cent (96 out of 147) of FHM patients had FHM with co-occurrence of one or two other migraine forms. Of these, 11% (16 out of 147) had FHM with co-occurrence of migraine without aura (MO), 39% (57 out of 147) had FHM with co-occurrence of MA, and 15% (23/147) had co-occurrence of both MO and MA.

FHM co-occurs with MO 1.6 times more often (39 compared to 23.8) than expected from the age and sex distribution in our material and the prevalence of MO in the general population, and FHM co-occurs with MA 7 times more often (80 compared to 11.5) than expected from the age and sex distribution in our material and the prevalence of MA in the general population. The 1.6 times increased risk of MO was not significant as compared with the general population [observed versus expected number of MO patients was 27% (39 out of 147; 95% CI: 0.2–0.34%) versus 16% (24 out of 147; 95% CI: 0.11–0.23%), respectively]. The 7 times increased risk of MA was significant as compared with the general population [observed versus expected number of MA patients was 54% (80 out of 147; 95% CI: 0.46–0.63%) versus 8% (12 out of 147; 95% CI: 0.04–0.14%), respectively].

Other symptoms and syndromes

Cerebellar ataxia in its chronically progressing form was identified in 10 FHM patients and two non-affected relatives. Eleven of these patients were from the same family. In this family, eight had ataxic speech, 11 had a wide-based ataxic gait, three had nystagmus, 10 had disturbed finger–nose and knee–heel test, and one patient had head tremor. The ataxia in this family was slowly progressive from 8–10 years of age and associated with progressive cerebellar atrophy, present on MRI scans in three patients and on CT scans in one patient (a total of five patients had been scanned). One FHM patient from another FHM family comprising two FHM affecteds had cerebellar ataxia characterized by wide-based ataxic gait and disturbed finger–nose and heel–knee test, no dysarthria, no nystagmus and no tremor, with an age at onset of 52 years.

Epilepsy was reported in 10 affected FHM patients (7%) and in five non-affected relatives (<1%). Of the latter, four came from FHM families where no FHM affected had epilepsy. One FHM family had three affected patients; another two affected and five FHM families had one patient affected with epilepsy. All patients reported generalized epileptic attacks. Only in two patients were these attacks occasionally associated with FHM attacks. Four FHM patients had had an MRI scan, which was normal.

Stroke was reported or identified outside FHM attacks by examination or neuroimaging investigation in five FHM patients. These patients were all unrelated and had been

affected with FHM since early childhood. Their FHM attacks had never previously caused any permanent neurological symptoms.

Coma was reported in two FHM patients from the same family, but only during a few of their FHM attacks. Both patients, according to the medical records, had CSF sterile pleocytosis and fever during these FHM attacks. None of them had any permanent neurological symptoms.

Discussion

FHM is a disorder with an interesting and complex symptomatology and a partially known genetic basis. As mentioned in the Introduction, several previous publications have described selected small and large families, but no population-based study has been available until now.

The population-based clinical characteristics gathered from the present study are compared with those of MA, where data from population-based studies are already available (Rasmussen and Olesen, 1992; Russell and Olesen, 1995; Stewart *et al.*, 1996; Sakai and Igarashi, 1997; Ulrich *et al.*, 1999). This comparison, together with existing genetic data, makes it reasonable to propose revised diagnostic criteria for FHM and to delineate its relationship to BM. It also allows important conclusions regarding clinical diagnosis, differential diagnosis and case ascertainment for genetic studies.

Methodological considerations

The methodology of the present study has been summarized briefly in Material and methods and has been described in detail elsewhere (L. L. Thomsen *et al.*, 2002, in press). In the latter, we estimated that the present material contains approximately half of all FHM patients in the Danish population of 5.2 million inhabitants. The material may be skewed towards large FHM families that were identified more easily by our screening procedures, but patients from large FHM families (≥ 4 affected) did not differ with regard to aura symptoms or headache characteristics compared with patients from small FHM families (< 4 affected). Undoubtedly, the present material is the most representative and largest sample of FHM patients ever collected (L. L. Thomsen *et al.*, 2002, in press).

Sex ratio

The overall male : female sex ratio was 1 : 2.5 (42M : 105F). There was a considerable difference in sex ratio among probands and among affected relatives [1 : 3.8 (9M : 35F) versus 1 : 2.1 (33M : 70F)]. This difference may be explained by the fact that females consult physicians more often (Rasmussen *et al.*, 1992) and/or that females had a higher participation rate.

The sex ratio among affected relatives was more equal in FHM families with more than four affected individuals.

These families had a male : female sex ratio among affected relatives of $\sim 1 : 2$, which is still a female preponderance compared with the sex ratio reported in selected FHM families (Haan *et al.*, 1994; Ahmed *et al.*, 1996; Ophoff *et al.*, 1996; Terwindt *et al.*, 1998b; Carrera *et al.*, 1999). The overrepresentation of women in FHM families could be due to ascertainment bias, but it more likely to reflect a difference in genetic disposition.

However, the overall difference in sex ratio of our material does not have any implications for our clinical results, since no significant differences were found with regard to aura symptoms, headache symptoms or basilar symptoms between genders.

Comparison of symptoms in FHM and MA

FHM has a lower age at onset compared with MA, which could be due to a higher genetic load. Lifetime number of attacks varied to the same degree in both conditions. The type of symptoms and their order of appearance were similar in FHM and MA. However, major clinical differences support that FHM and MA are separate entities. For example, FHM usually had more than two aura symptoms, and the duration of each was longer than in MA. Basilar-type migraine symptoms were often present during FHM attacks but not during MA, and FHM was accompanied more often by headache.

Relationship between FHM and BM

Based on our semi-structured telephone interview, 69% of FHM patients also fulfilled IHS criteria for BM. The symptom ataxia was taken into account when defining if IHS criteria for BM were fulfilled, because patients most probably are unable to distinguish if ataxia is caused by reduced strength of a limb, reduced coordination due to sensory loss or is of cerebellar origin. Interestingly, previous studies have shown that BM symptoms frequently are present in FHM (66%), but did not find basilar-type symptoms in 33 patients with MA (Haan *et al.*, 1995). Do BM symptoms originate from bilateral cortical dysfunction or from brainstem dysfunction? Looking at our BM symptoms (Table 5), both of these are possible. Only a small fraction of BM symptoms originated with a high degree of certainty from the brainstem. Furthermore, if brainstem dysfunction were responsible for the aura symptoms in FHM, why do crossed symptoms (symptoms in the limbs contralateral to cranial nerve symptoms) occur so seldom (in our study only in one patient), and why have crossed symptoms only been reported twice during FHM attacks previously (Ohta *et al.*, 1967; Haan *et al.*, 1995)? Unconsciousness, a symptom frequently reported during BM attacks, was, in our study, only reported by two patients and only in a few of their attacks. If they originated from the brainstem, unconsciousness should be expected to be more frequent. In conclusion, our data show that BM symptoms definitely can originate from the

brainstem but may be caused more often by simultaneous or almost simultaneous dysfunction of the hemispheres. This view is supported by cerebral blood flow studies and by EEG recordings during attacks (Symonds, 1952; Heyck, 1973; Gastaut *et al.*, 1981; O'Hare *et al.*, 1981; Olesen *et al.*, 1981; Lee *et al.*, 1996).

The BM symptoms during FHM attacks were typically (88%) reported during the end of the aura, which indicates that, if the FHM attack is initiated by unilateral cortical spreading depression, it spreads to the brainstem and/or to the opposite hemisphere during a late phase of the attack. Since cortical spreading depression can only spread in grey matter, a transcallosal spread would have to be neurogenic, similar to mirror foci seen in the opposite hemisphere of an epileptic focus.

FHM, cerebellar ataxia, epilepsy and coma

Based on the literature, two subforms of FHM families exist; pure FHM in 80% and FHM families with cerebellar symptoms in 20%. The latter all have a mutation in the *CACNA1A* gene on chromosome 19p13.

In our material, the expected number of FHM families with cerebellar symptoms would be eight or nine, but we found only two. Thus, ataxia seems to be infrequent in the Danish population compared with worldwide. Whether this is due to a different genetic mechanism or whether *CACNA1A* mutations are rarely associated with ataxia in Denmark is not known so far.

In one FHM family with cerebellar symptoms, 50% (one out of two) of FHM affecteds had cerebellar symptoms and, in the other FHM family, 82% (nine out of 11) had FHM and cerebellar symptoms, while two unaffected relatives had cerebellar symptoms. The penetrance of ataxia in our material seems to be in agreement with the previous literature.

Epilepsy was present in 7% (95% CI: 3–11%) of affected FHM patients. The point prevalence of epilepsy in Denmark has been estimated previously to be ~1% (Skaarup, 1997). Non-affected relatives had no increased risk of epilepsy. We thus confirm previous observations of an association between FHM and epilepsy (Terwindt *et al.*, 1998a).

Coma was present in two FHM patients, which is surprisingly few considering that this phenomenon has been reported in as many as one-third of FHM patients with a *CACNA1A* mutation. This again suggests that there may be a lower frequency of patients with a *CACNA1A* mutation in the Danish population compared with other countries.

Co-occurrence of other migraine forms

FHM co-occurs with MA seven times more often than expected, when considering the age and sex distribution in our material and the prevalence of MA in the general population. In the previous literature, it has been reported that ~10% of FHM patients have co-occurrence of MA and ~20–30% of FHM patients have co-occurrence of MO (O'Hare

et al., 1981; Ducros *et al.*, 2001). Compared with these data, we find a similar percentage of FHM patients with co-occurrence of MO (26%), which was not significant compared with the general population, but a higher overall percentage of FHM patients with co-occurrence of MA (54%), which was significant compared with the general population. Our data suggest that mutations causing FHM may also cause attacks of MA. However, whether they may cause only MA attacks in other patients remains uncertain.

Consequences for headache classification, case ascertainment and clinical diagnosis

In our families and in previous publications (Ducros *et al.*, 1995, 1997; Gardner *et al.*, 1997), there are several cases with reduced penetrance. It is therefore suggested to change the requirement for an affected first-degree relative to a first- or second-degree relative.

Our results show that the criteria of FHM can be more strict, requiring at least two aura symptoms to be present, and that both symptoms should be 'typical' aura symptoms. In the present classification, it is stated that aura symptoms in FHM may be prolonged. The present data show that this is most often the case and it therefore seems relevant to accept a duration of each symptom of 24 h. A lower limit would exclude too many otherwise typical attacks. The duration of aura symptom of 24 h should not be obligatory, because some previous publications have reported that the aura can last >24 h during typical FHM attacks. The gradual development of aura symptoms is essential, and caution is necessary in diagnosing hemiplegic migraine with acute onset aura. The gradual progression of the motor, sensory and visual aura symptoms usually took ~60 min. The presence of headache is highly typical but should not be obligatory, because two of 147 of our patients together with other published cases never had headache in association with hemiplegic aura symptoms. Therefore, we suggest the presence of headache and the duration of 24 h to be two of three subcriteria, of which at least two should be fulfilled. According to the present IHS criteria, the term 'some degree of hemiparesis' has been required to fulfil the criteria of FHM. However, this term could be interpreted as requesting a hemiparesis (some degree of paresis of an arm *and* a leg) or as paresis of an arm *or* a leg. In the present material, some cases had one extremity affected and others had both extremities affected unilaterally. Therefore the term '*motor weakness*' (meaning affection of any degree of an arm and/or a leg) is included in the proposed new criteria for FHM (Table 8). A clarification of the sensitivity and specificity of our proposed criteria will have to be done in future prospective studies.

Finally, it should be made clear in a comment that the presence of basilar migraine symptoms should not lead to a BM diagnosis, when concomitant with motor weakness, because BM symptoms are typically a part of FHM symptomatology. We suggest revision of IHS criteria for

Table 8 Proposed new diagnostic criteria for familial hemiplegic migraine

Description	Migraine with aura including motor weakness and where at least one first- or second-degree relative has migraine aura including motor weakness
Diagnostic criteria	<p>A. At least two attacks fulfilling B–E</p> <p>B. Fully reversible symptoms including motor weakness and at least one of the following: visual, sensory or speech disturbance</p> <p>C. At least two of the following:</p> <ol style="list-style-type: none"> 1. At least one aura symptom develops gradually over at least 5 min or symptoms occur in succession 2. Each aura symptom lasts <24 h 3. Some degree of headache is associated with the aura <p>D. At least one first- or second-degree relative has migraine aura including motor weakness fulfilling criteria A, B, C and E</p> <p>E. Not attributed to another disorder</p>

BM by adding an extra criterion: not associated with motor weakness, as shown in Table 9. The high frequency of BM symptoms in FHM suggests that pure BM patients, without motor weakness, may have the same genetic basis as FHM, as previously pointed out by others (Haan *et al.*, 1995). This remains a hypothesis until genetic confirmation becomes available.

Consequences for clinical diagnosis and differential diagnosis

With or without the proposed new diagnostic criteria, our data allow a more precise clinical diagnosis of FHM. Thus, we have shown that aura symptoms in FHM are very typical, that FHM patients always have at least two aura symptoms per attack and that headache almost always occurs in a close temporal relationship to the aura symptoms. The data also show that FHM aura symptoms virtually never occur without visual aura symptoms, that FHM is expressed before age 35 years and that FHM patients seldom have attacks after age 50 years. Furthermore, FHM frequently co-occurs with MA and/or MO.

FHM is distinguished from transient ischaemic attack (TIA) by the gradual development and progression of aura symptoms in contrast to the instant onset of symptoms in TIA (Fisher, 1980). Progression from one aura symptom to another strongly supports a migraine diagnosis. Several patients in the present study reported that the sensory and sometimes the motor symptoms disappeared in the same order as they appeared (i.e. the aura symptom that appeared first also disappeared first). Theoretically, this would be the opposite in TIA and stroke (vascular events), a characteristic clinical feature that can help in making the correct diagnosis.

Epilepsy may mimic FHM when there is a Jacksonian march and post-ictal paresis and headache. Our data show that the duration of the gradual progression of the aura symptoms is 60 min on average, which is never seen in epilepsy, and also that visual symptoms almost always

Table 9 Proposed new diagnostic criteria for basilar-type migraine (BM)

Description	Migraine with aura where symptoms clearly originate from the brainstem or from simultaneous affection of both hemispheres and where no motor weakness is present
Diagnostic criteria	<p>A. Fulfils criteria for 1.2 (migraine with aura)</p> <p>B. Two or more aura symptoms of the following types:</p> <ul style="list-style-type: none"> Dysarthria Vertigo Tinnitus Decreased hearing Double vision Ataxia Decreased level of consciousness Simultaneous bilateral visual symptoms in both the temporal and nasal field of both eyes Simultaneous bilateral paresthesias <p>C. Not associated with motor weakness*</p> <p>D. Not attributed to another disorder</p>

*If motor weakness is present, code hemiplegic migraine.

accompany the paresis, which almost never happens in epilepsy.

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