J Headache Pain (2001) 2:S83–S86

KEY NOTE LECTURE

Michael Bjørn Russell

Familial occurrence in primary headaches

M.B. Russell (✉)
Department of Neurology,
University of Copenhagen,
Gentofte Hospital,
2900 Hellerup, Copenhagen, Denmark
e-mail: mbr@dadlnet.dk
Tel.: +45-39-773977
Fax: +45-45-859220

Abstract This paper reviews the literature of genetic epidemiology in primary headaches. *Migraine without aura* and *migraine with aura* are distinct disorders. Both are caused by a combination of genetic and environmental factors. *Tension-type headache*. The episodic form is most likely non-genetic, while the chronic form is caused by a combination of genetic and environmental factors. *Cluster headache* has previously not been thought to be genetic. However, first degree relatives of cluster headache sufferers have a 14–46 fold significantly increased risk of cluster headache, compared to the general population.

Key words Genetics • Migraine • Cluster headache • Tension-type headache

Introduction

The classification of the International Headache Society defines primary headaches as migraine, tension-type headache and cluster headache [1]. Familial occurrence has been reported for all the primary headaches, but only migraine has been thought to be inherited based on a frequent positive family history. However, a positive family history is imprecise, because it does not specify number of affected, family size, or relation to the proband [2]. Nor does it include a clinical interview of the relatives by a physician [3]. The high prevalence of migraine causes a positive family history simply by chance in >80% of probands with six first-degree relatives, i.e. parents, siblings and children, and one or both parents are affected in >40% of the families.

The present paper reviews the literature on familial occurrence in primary headaches.

Migraine

Clinical, epidemiological, pathophysiological and genetic differences indicate that *migraine without aura* and *migraine with aura* are distinct entities. Thus, the two types of migraine are analysed separately. Table 1 shows the relative risk of migraine without aura and migraine with aura in different genetic epidemiological surveys [4–7]. The interviewers of the Danish [4] and American [6] surveys were blind to the diagnostic status of the proband when interviewing the family members. The probands and first-degree relatives of the Danish survey were interviewed by one physician [4]. The probands of the American survey were interviewed and examined by a physician, while the first-degree relatives were telephone-interviewed by lay interviewers about their most severe type of headache [6]. The American study changed the diagnostic criteria for migraine with aura to be

Table 1 Participants in genetic epidemiological surveys of migraine without aura (MO) and migraine with aura (MA)

Disease in probands	Study population	Disease in first-degree relatives	Probands, n	First degree relatives, n		Relative risk[1]	Population relative risk[2]	95% Confidence interval
				Affected	Total			
Migraine with aura								
Mochi et al. [5]	Clinic	MO	34	64	171	3.62	–	1.10–6.14
Russell and Olesen [4]	General	MO	126	102	354	–	1.86	1.56–2.16
	General	MA	126	42	354	–	1.44	1.03–1.85
Stewart et al. [6][3]	General	MO	45	30	156	1.43	–	0.83–2.47
	General	MA	45	10	156	2.36	–	0.87–6.38
Migraine with aura								
Mochi et al. [5]	Clinic	MA	35	13	144	6.95	–	3.15–10.75
Russell and Olesen [4]	General	MA	127	111	359	–	3.79	3.21–4.38
	General	MO	127	56	359	–	1.02	0.77–1.26
Kalfakis et al. [7]	Clinic	MA	60	58	328	11.85	–	7.00–16.70
Stewart et al. [6][3]	General	MA	28	3	87	1.24	–	0.28–5.47
	General	MO	28	17	87	1.41	–	0.71–2.77

[1] First-degree relatives of probands with migraine compared to first-degree relatives of probands who had never had migraine

[2] First-degree relatives of probands with migraine compared to the risk of migraine in the general population

[3] Probands were interviewed by a physician, while first-degree relatives were interviewed by lay interviewers

Table 2 Numbers of concordant and discordant same-gender monozygotic (MZ) and dizygotic (DZ) twin pairs. Concordance rates are in percentages

	Men		Women		Overall	
	MZ	DZ	MZ	DZ	MZ	DZ
Migraine without aura[1]						
Concordant pairs, n	8	6	30	41	38	47
Discordant pairs, n	39	69	60	141	99	210
Pairwise concordance rate, %	17	8	33	23	28	18
Probandwise concordance rate, %	29	15	50	37	43	31
Migraine with aura[2]						
Concordant pairs, n	12	10	14	6	26	16
Discordant pairs, n	21	48	30	70	51	118
Pairwise concordance rate, %	36	17	32	8	34	12
Probandwise concordance rate, %	53	29	48	15	50	21

[1] From Gervil et al. [8, 9]
[2] From Ulrich et al. [10, 11]

similar to the headache characteristics of migraine without aura. However, the diagnosis migraine with aura does not require specific headache characteristics [1]. This probably caused an underestimation of migraine with aura in the American study, since the headache is less severe in migraine with aura than in migraine without aura. Furthermore, for an unerring diagnosis interviews by physicians are preferred. The Greek [7] and Italian [5] studies were based on clinic populations, which may have caused bias.

Table 2 shows the number of concordant and discordant twin pairs from a Danish population-based twin study. The study included 1013 monozygotic and 1667 dizygotic twin pairs of the same gender [8–11]. The pair-wise concordance rate was significantly higher among monozygotic than dizygotic twin pairs in both types of migraine (migraine without aura $p<0.05$ and migraine with aura $p<0.001$). Analysing men and women separately showed a similar trend. The proband-wise concordance rates were 31% and 21% among dizygotic twin pairs with migraine without aura and migraine with aura, respectively. This risk is comparable to the 30% and 27% recurrence risk in Danish siblings [4]. Thus, genetic epidemiological surveys and twin studies suggest that both types of migraine are caused by a combination of genetic and environmental factors.

Tension-type headache

Until recently a genetic factor had not been suspected in tension-type headache. The high prevalence of episodic tension-type headache causes a positive family history simply by chance in >99% of families with an affected proband and four first-degree relatives. One or both parents will be affected by chance in >94% of the families. Episodic tension-type headache is most likely a heterogeneous disorder. The uniform symptomatology makes it likely that nociceptive mechanisms are shared, but can be activated by different mechanisms. It may be caused by multiple genes in a concerted action with environmental factors or it may be non-genetic.

Only a single genetic epidemiological study has investigated the familial aggregation of chronic tension-type headache [12, 13]. It included 122 probands from a headache clinic meeting the criteria of the International Headache Society for chronic tension-type headache [1]. The probands' first-degree relatives and spouses were interviewed by a neurological resident. The risk of familial occurrence was assessed by estimating the population relative risk. Compared with the general population, first-degree relatives had a 3.1-fold significantly increased risk of chronic tension-type headache, while spouses had no increased risk of chronic tension-type headache [12, 13]. This result indicates the importance of a genetic factors.

Cluster headache

The literature provides more complete information in four genetic epidemiological studies [14-18]. The first study, a Danish genetic epidemiological survey, included 370 probands [14, 15]. A physician interviewed probands with a positive family history and all possibly affected relatives

alive. Compared with the general population, first-degree relatives had a 14-fold significantly increased risk of cluster headache after standardisation for age and gender. Second-degree relatives had a 2-fold significantly increased risk of cluster headache.

An American survey included 300 mainly Caucasian probands [16]. The probands reported about their possibly affected first-degree relatives, but the diagnosis was not confirmed by an interview. Compared with the general population, first-degree relatives had a 46-fold significantly increased risk of cluster headache after standardisation for gender.

An Italian study included 222 probands [17]. The interviews were performed by neurologists. A positive family history among first- and second-degree relatives was found in 2.3% of the families. Another Italian study included 220 probands [18]. All possibly affected relatives were telephone-interviewed by physicians. Compared with the general population, first-degree relatives has a 39-fold significantly increased risk of cluster headache after standardisation for age and gender. Second-degree relatives had an 8-fold significantly increased risk of cluster headache. The latter study made a more throughout search for relatives, which may explain the higher familial occurrence.

All the studies selected probands from clinic populations. This may affect the representativeness of the study population. However, most likely it only has minor significance, since 92% (24/26) of the affected relatives alive had at some time consulted a physician and/or a neurologist because of their cluster headache [15]. This is a much higher consultation rate than found among migraineurs (56%) and tension-type headache sufferers (16%) [19]. The significantly increased familial risk strongly suggests a genetic cause for cluster headache. Theoretically, a shared environment can produce relative risks of the magnitude observed for cluster headache only under extreme conditions [20].

References

1. Headache Classification Committee of the International Headache Society. (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 8:1–96
2. Russell MB (1997) Genetic epidemiology of migraine and cluster headache. Cephalalgia 17:683–701
3. Russell MB, Fenger K, Olesen J (1996) The family history of migraine. Direct versus indirect information. Cephalalgia 16:156–160
4. Russell MB, Olesen J (1995) Increased familial risk and evidence of genetic factor in migraine. BMJ 311:541–544
5. Mochi M, Sangiorgi S, Cortelli P, Carelli V, Scapoli C, Crisci M, Monari L, Pierangeli G, Montagna P (1993) Testing models for genetic determination in migraine. Cephalalgia 13:389–394
6. Stewart WF, Staffa J, Lipton RB, Ottman R (1997) Familial risk of migraine: a population-based study. Ann Neurol 41:166–172
7. Kalfakis N, Panas M, Vassilopoulos D, Malliara Loulakaki S (1996) Migraine with aura segregation analysis and heritability estimation. Headache 36:320–322
8. Gervil M, Ulrich V, Kaprio J, Olesen J, Russell MB (1999) The relative role of genetic and environmental factors in migraine without aura. Neurology 53:995–999
9. Gervil M, Ulrich V, Kyvik KO, Olesen J, Russell MB (1999) Migraine without aura: A population based twin study. Ann Neurol 46:606–611
10. Ulrich V, Gervil M, Kyvik KO, Olesen J, Russell MB (1999) Evidence of a genetic factor in migraine with aura: A population-based Danish twin study. Ann Neurol 45:242–246
11. Ulrich V, Gervil M, Kyvik KO, Olesen J, Russell MB (1999) The inheritance of migraine with aura estimated by means of structural equation modelling. J Med Gen 36:225–227
12. Østergaard S, Russell MB, Bendtsen L, Olesen J (1997) Comparison of first degree relatives and spouses of people with chronic tension-type headache. BMJ 314:1092–1093
13. Russell MB, Østergaard S, Bendtsen L, Olesen J (1999) Familial occurrence of chronic tension-type headache. Direct versus indirect information. Cephalalgia 19:207–210
14. Russell MB, Andersson PG, Thomsen LL (1994) Familial occurrence of cluster headache. Genet Epidemiol 11:305–306 (abstract)
15. Russell MB, Andersson PG, Thomsen LL (1995) Familial occurrence of cluster headache. J Neurol Neurosurg Psychiatry 58:341–343
16. Kudrow L, Kudrow DB (1994) Inheritance of cluster headache and its possible link to migraine. Headache 34:400–407
17. Montagne P, Mochi M, Prologo G, Sangiorgi S, Pierangeli G, Cevoli S, Cortelli P (1998) Heritability of cluster headache. Eur J Neurol 5:343–345
18. Leone M, Russell MB, Rigamonti A, Attanasio A, Grazzi L, D'Amico D, Usai S, Bussone G (2001) Increased family risk of cluster headache. Neurology (*w*)
19. Rasmussen BK, Jensen R, Olesen J (1992) Impact of headache on sickness absence and utilisation of medical services: a Danish population study. J Epidemiol Community Health 46:443–446
20. Khoury MJ, Beaty TH, Liang K-Y (1982) Can familial aggregation of disease be explained by familial aggregation of environmental risk factors? Am J Epidemiol 127:674–683