Familial occurrence of cluster headache

Michael Bjørn Russell, Poul Gertz Andersson, Lars Lykke Thomsen

Abstract
The familial occurrence of cluster headache was assessed in 421 patients with cluster headache, diagnosed according to the operational diagnostic criteria of the International Headache Society. The patients were recruited from a neurological clinic and two departments of neurology, covering east central Jutland and Copenhagen County respectively. They received a mailed questionnaire regarding the presence of cluster headache among their first and second degree relatives. All possibly affected relatives were interviewed by telephone. The response rate to the questionnaire was 88% (370/421). Seven patients belonged to three families. A positive family history of cluster headache was found in 7% (25/366) of the families. Compared with the general population, the first and second degree relatives of the 370 patients with cluster headache had a 14-fold and twofold increase in the risk of having cluster headache after standardisation for sex and age. This increase in familial risk strongly suggests that cluster headache has a genetic cause.

Keywords: cluster headache; familial aggregation; genetics

Cluster headache is characterised by recurrent, unilateral attacks of headache of great intensity and brief duration, accompanied by local signs and symptoms of autonomic dysfunction.1 The attacks occur in series lasting weeks or months, so called cluster periods. The aetiology and pathogenesis remain largely unknown. Cluster headache has not previously been considered to be inherited.2-3 A positive family history of cluster headache was found, however, among first degree relatives (parents, siblings, children) in 51 of 1406 families.4-15 As cluster headache is rare it suggests that it may be an inherited disorder, even though "a positive family history" is an imprecise term.

The aim of the study was to determine the relative risk of cluster headache in first and second degree relatives of patients with cluster headache, with sex and age taken into account.

Materials and methods

DATA COLLECTION
Patients (probands) of Danish origin, alive, and with a diagnosis of cluster headache according to the criteria of the International Headache Society (IHS)1 were included. The probands were recruited from a neurological clinic (342 patients), covering Århus and east central Jutland, and a headache research unit in a university hospital (60 patients) and a department of neurology (19 patients), both covering Copenhagen County. A detailed semistructured history of headache was obtained by neurologists or neurological residents trained in headache diagnoses. All probands had a physical and a neurological examination to exclude other medical or neurological disorders. The probands received a mailed questionnaire. If the first questionnaire evoked no response, a second was mailed. The probands were asked about the number and sex of their first and second degree relatives, the age of their first degree relatives, and if any of their relatives had ever experienced cluster headache. Probands with a positive family history were interviewed by telephone (by MBR). Subsequently, all possibly affected relatives were interviewed by telephone. Only relatives fulfilling the criteria of IHS had a diagnosis made of cluster headache. The probands and the closest family members were interviewed about possibly affected dead relatives. A diagnosis of cluster headache was made if this second hand history confirmed the diagnosis according to the criteria of the IHS, with the exception of criterion C, which specifies that headache is associated with at least one of the following signs, which have to be present on the panside: conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, or eyelid oedema.

The project was approved by the Danish ethics committees.

STATISTICAL METHODS
The risk of familial occurrence was assessed by estimating the population relative risk of the disease in specified groups of relatives.

<table>
<thead>
<tr>
<th>Age (°)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>20-39</td>
<td>109</td>
<td>24</td>
</tr>
<tr>
<td>40-59</td>
<td>153</td>
<td>40</td>
</tr>
<tr>
<td>≥60</td>
<td>160</td>
<td>43</td>
</tr>
<tr>
<td>Overall prevalence</td>
<td>369</td>
<td>99</td>
</tr>
</tbody>
</table>

Table 1 Sex and age specific frequency of cluster headache per 100 000 inhabitants
Table 2  Sex and age standardised risk of cluster headache among first and second degree relatives of probands with cluster headache relative to the population risk

<table>
<thead>
<tr>
<th>No of affected relatives</th>
<th>Population relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed (O)</td>
</tr>
<tr>
<td>First degree relatives</td>
<td></td>
</tr>
<tr>
<td>Parents</td>
<td>710</td>
</tr>
<tr>
<td>Siblings</td>
<td>835</td>
</tr>
<tr>
<td>Children</td>
<td>660</td>
</tr>
<tr>
<td>Second degree relatives</td>
<td></td>
</tr>
<tr>
<td>Male/relative</td>
<td>1751</td>
</tr>
<tr>
<td>Female/relative</td>
<td>454</td>
</tr>
</tbody>
</table>

Table 3  Effect of generation and sex of the proband on the population relative risk of cluster headache among first degree relatives of probands with cluster headache

<table>
<thead>
<tr>
<th>No of first degree relatives</th>
<th>No of affected relatives</th>
<th>Population relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed (O)</td>
<td>Expected (E)</td>
</tr>
<tr>
<td>Generation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siblings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex of proband/relative:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male/relative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female/relative</td>
<td></td>
<td></td>
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</tbody>
</table>

Numbers in parentheses are those not alive with a diagnosis of cluster headache (see definitions in methods).

The risk was calculated according to the equation:

Prob(relative is affected | proband is affected) = Prob(random member of the population is affected)

A family aggregation is implied when this risk ratio significantly exceeds 1.

An epidemiological survey of cluster headache showed overall lifetime prevalence of cluster headache of 69 per 100 000 habitants. The sex and age specific frequency of cluster headache was based on the sex distribution and age at onset among our probands (table 1). Because the frequency of cluster headache depends on sex and age, the value of the denominator was adjusted according to the distribution of sex and age in the groups of relatives studied (first degree relatives only, because the ages of the second degree relatives were unknown). Hence, this standardised population relative risk was estimated by dividing the observed number of affected first and second degree relatives by the expected number according to the frequency in the population. The expected number was calculated by adding the products of the current sex and age specific rates and the number of relatives within each corresponding sex-age category. The adjusted population relative risk of cluster headache was estimated separately for the first and second degree relatives. The population relative risk was also calculated separately for parents, sibs, and children and for first degree relatives of male and female probands.

The 95% confidence intervals (95% CIs) of the frequencies of first and second degree relatives and the population relative risks of the different constellations were estimated with the assumption that the numbers affected in the group of relatives followed a Poisson distribution. If more than one proband occurred in the same family, the youngest proband was regarded as the index person, and the family was only counted once.

Results

Adequate questionnaire information was obtained from 370 of the 421 probands with cluster headache (88%). Of the 370 probands, 78 (21%) were women 15 to 81 (mean 47) years old and 292 (79%) were men 20 to 87 (mean 49) years old. Of the 370 probands, 11 were adopted and four had an unknown father. The probands had a total of 2205 first (1065 females and 1140 males) and 6223 second degree relatives (3034 females and 3199 males). A positive family history of cluster headache was reported by 47 probands (six females and 41 males). Seven of the probands belonged to three families. The interviews by telephone confirmed a family history of cluster headache in 25 of the 366 families (7%). Twenty first degree (seven females and 13 males) and six second degree relatives (two females and four males) had cluster headache. Six first degree relatives (three females and three males) and four second degree relatives (two females and two males) were dead, but a clear history from relatives strongly suggests that they had cluster headache. The frequencies of cluster headache were 1.2% (26/2205) among first degree relatives and 0.2% (10/6223) among second degree relatives. The population relative risk of cluster headache was significantly increased in first and second degree relatives (table 2). Table 3 shows the population relative risk in the different generations and among relatives to male and female probands.

Discussion

METHODOLOGICAL CONSIDERATION

Three epidemiological studies of cluster headache have been published. The first survey was based on 9803 18 year old men from east central Sweden; the second was a survey of 21 792 inhabitants of the Republic of San Marino, and the third included 6476 Olmsted County residents. We used the prevalence of cluster headache in San Marino as a reference for the Danish population. It is hazardous to extrapolate the findings in 18 year old men to a whole population. The Olmsted County study is imprecise, because patients were included with only one attack, with attacks not clearly within a 15 to 180 minute duration, and the diagnosis was based on case records not confirmed by a clinical interview. The suspected diagnosis of cluster headache was confirmed in only 14 of the 39 neurological case records in the San Marino survey.

The probands were selected from a neurological clinic and two departments of neurology, and not from the general population. This could cause ascertainment bias towards patients with more severe cluster headache, but probably did not, as 92% (24/26) of the affected first and second degree relatives alive had consulted a physician or a neurologist because of their cluster

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headache. The frequency of cluster headache among first and second degree relatives in our study is probably underestimated due to several factors: (1) probands may fail to report familial occurrence, as did one nephew who was only detected because his uncle was also a proband; (2) probands adopted or with an unknown father may be familial cases; (3) exclusion of 40 dead patients, at least two of whom were familial cases (a father and a son); (4) the diagnosis cluster headache was largely unknown in Denmark 30 years ago. The underestimation probably affects the older more than the younger generation. An example from our study was the father to a male proband. The father had been told that he had trigeminal neuralgia and had several operations for this condition, but the son believed the symptoms were similar to his own. This was confirmed by interviewing the father. Other cases may have been missed on this account. The diagnosis of cluster headache in dead relatives was made, with the exception of the IHS criterion C, as the second hand history was uncertain about autonomic symptoms relating to pain. The dead relatives may well have experienced these symptoms. The interview was otherwise very restrictive and only dead relatives with a clear second hand history about attack location, duration, and cluster periods had the diagnosis. A female second degree relative had only one cluster period (one to two attacks per day in a cluster of three months duration) and a male proband had no autonomic symptoms on the headache side. They were included even though one of the IHS criteria was not fulfilled. The male proband is a physician, and it is almost certain that he did not miss autonomic symptoms. Their inclusion is justified because the cluster period in the female was absolutely typical and autonomic symptoms are lacking in a few otherwise typical patients.\textsuperscript{20-22} Nineteen probands reported familial occurrence of cluster headache that was not confirmed by the interview. This was due to relatives with migraine. We have no familial information on those not responding to the questionnaire. Assuming these 51 persons had no affected relatives and a proportional number of first and second degree relatives as the 370 probands, the results would theoretically be weaker than 12% (51/421). A combination of these points most likely causes underestimation of the effect found.

PRESENT RESULTS

Our main finding is that first and second degree relatives of probands with cluster headache had a 14-fold and twofold increased risk of having cluster headache compared with the general population. This strongly suggests a genetic cause for cluster headache. Theoretically, a shared environment will produce relative risks of the magnitude we found for cluster headache only under unlikely, extreme conditions.\textsuperscript{23} Further support for a genetic factor is concor-
dance of cluster headache in five pairs of monozygotic twins,\textsuperscript{10-26} and familial occurrence of cluster headache in three generations,\textsuperscript{27} although publication itself introduces selection bias.\textsuperscript{28} Even though the risk of cluster headache was increased in first and second degree relatives, most cases are probably sporadic. Proper assessment of this question requires a complex segregation analysis.\textsuperscript{29} Future focus on familial cases will most likely concentrate on the identification of the gene(s).

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