A comparison of familial and sporadic migraine in a headache clinic population

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Summary

We compared the clinical, psychological and pharmacological characteristics of patients with familial migraine and patients with sporadic migraine. Five hundred and thirty consecutive new patients attending our Headache Center over a two-year period were involved in the study. The patients were divided into two groups: A. Familial migraine (famM) – at least one first-degree relative affected; B. Sporadic migraine (spoM) – no first-degree relative affected. Four hundred and twenty-four patients (80%) fulfilled the criteria for famM and 106 (20%) for spoM. The patients with famM showed a significantly (p<0.01) earlier age at onset of the disease. No significant difference in all the remaining features examined was found. Our data suggest that famM and spoM represent a single disease entity.

KEY WORDS: Age at onset, clinical features, familial, genetics, migraine.

Introduction

Migraine is a common neurovascular disorder that affects approximately 10% of the general population (1). There is substantial evidence for the role of genetic factors in the etiology of migraine. First-degree relatives of patients with migraine have a significantly higher risk of having the disease in comparison with controls (2,3). Several studies have demonstrated that monozygotic twins have a significantly higher concordance rate for the disease than dizygotic twins (4,5). Finally, mutations in a brain-specific P/Q-type Ca^{2+} channel α1-subunit gene, the CACNA1A gene on chromosome 19p3, have been shown to be involved in some cases of familial hemiplegic migraine (FHM) (6). However, both twin studies (7) and population-based epidemiological studies (8) have suggested that genetic factors account for only 50% of all the migraine cases in the general population. The remaining patients have no affected first-degree relative and are considered sporadic cases.

At present, no study comparing famM and spoM is available. Several studies have clearly shown that migraine is a heterogeneous disorder: pain intensity, attack frequency, disability, duration of the disease, frequency of accompanying symptoms and all the remaining clinical symptoms of the disease are highly variable both in the single patient and in different patients (9,10). The purpose of our study was to look for possible phenotypic differences between famM and spoM. In order to do so, we compared the clinical, psychological and pharmacological characteristics of migraine patients with and without affected first-degree relatives.

Materials and methods

Subjects

Consecutive new patients attending, for the first time, the Headache Center of the University of Turin (Italy) over a 24-month period (January 1997 - December 1998) were involved in this prospective study. The diagnosis of headache was made according to the International Headache Society (IHS) criteria (11). Five hundred and thirty patients (406 women, 124 men; age range 6-79 years) were selected for the study.

The patients were carefully interviewed, using a standardized questionnaire, to ascertain the occurrence in first-degree relatives of severe headaches with symptoms characteristic (IHS criteria) of migraine. The patients were divided into two groups: A. Familial migraine (famM) – at least one first-degree relative affected; B. Sporadic migraine (spoM) – no first-degree relative affected. Four hundred and twenty-four patients (80%) fulfilled the criteria for famM and 106 (20%) for spoM. The patients with famM showed a significantly (p<0.01) earlier age at onset of the disease. No significant difference in all the remaining features examined was found. Our data suggest that famM and spoM represent a single disease entity.

KEY WORDS: Age at onset, clinical features, familial, genetics, migraine.

Psychological testing

Psychological evaluation of the patients was performed using the State-Trait Anger Expression Inventory Scale
the Beck's Depression Inventory (BDI) (12), the State and Trait Anxiety Inventory (STAI) tests (13) and the Cognitive Behavioral Assessment (CBA) (14). For the purposes of this study, only the BDI, and STAI X-1 and X-2 scores were used. The maximum normal score on the BDI in the Italian adult population is 12 in women and 10 in men. The normal STAI X-1 (state anxiety) range is 45±12.1 in Italian adult women and 40±10.0 in men, while the normal range of the STAI X-2 (trait anxiety) is 46.1±11.5 in women and 39.5±9.3 in men.

Placebo and nocebo tests

The patients underwent either the placebo or the nocebo test, according to the presence or absence of headache at their first visit to the Headache Center. Patients undergoing the placebo test were given a white talcum powder tablet and told it was a potent analgesic drug; those undergoing the nocebo test received the same tablet but were told that it could induce headache. Headache severity was scored on a 4-point scale (0 = no pain, 3 = maximum pain). The patients returned to the Headache Center 1 week later to report the test response. The criterion for a placebo positive response was a 2-point reduction in headache intensity 4 hours following the talcum administration. The criterion for a nocebo positive response was the induction of a 2- or 3-point headache attack during the same period of time. Patients without a clear-cut response (difference of only 1 point) were defined as uncertain.

Pharmacological tests

These tests were performed only in the patients not under prophylactic antimigraine therapy. The selected patients were instructed to treat their next three migraine attacks with a triptan (sumatriptan 100 mg or zolmitriptan 2.5 mg per os) (triptan test) and to record headache relief in their headache diary. Three months later, the patients performed the NSAIDS test (aspirin 500 mg or indomethacin 50 mg per os) in three migraine attacks. Patients unable to record headache attacks correctly in their diary were eliminated from the study. Patients who experienced headache relief two hours after taking the drug in at least two-thirds of the treated attacks were defined as responders. Patients with no headache relief were defined as non-responders. In the remaining cases, the patients were classified as uncertain.

Statistical analysis

The statistical evaluation was performed using GBSTAT - version 6.5. The distribution of the data was analyzed using the D’Agostino test. Those found to follow a normal distribution were analyzed using unpaired Student’s t test while non-parametric data were analyzed using the Mann Whitney U test. Proportions were analyzed using the Fisher exact test and $\chi^2$ test. The level of statistical significance was set at $p<0.05$.

Results

Four hundred and twenty-four patients (324 females, 100 males) fulfilled the criteria for famM and 106 (82 females, 24 males) for spoM. Table I compares the demographic and clinical characteristics of the two patient groups. Age at onset of the disease was found to be significantly (p=0.001) lower in patients with famM. No significant difference emerged in any of the other features examined. Psychological tests were performed correctly by 467 (88.1%) of the patients. Table II shows the BDI, STAI X-1 and STAI X-2 test scores. No significant difference between FamM and SpoM patients was observed. Table III displays the results of the placebo/nocebo test and of the pharmacological tests. The placebo/nocebo test was performed by 460 patients (86.8 %): 191 (41.5%) and 269 (58.5%) respectively. A placebo positive test was reported by 29.5% of the patients and a nocebo positive test by 15.6% of the patients. No significant difference in the responses to these tests was observed between FamM and SpoM patients. As regards the pharmacological testing, 61.4% performed the triptan test and 68.4% performed the NSAIDS test. No significant difference in the responses to the drugs tested was observed between patients with FamM or SpoM.

In additional analyses, a comparison between migraine patients with and without aura was performed. No significant difference emerged between familial and sporadic cases.

Discussion

There are some limitations to our study that could have influenced the results. All the analyses were performed on patients attending a Headache Center. Previous studies have demonstrated that headache patients seeking medical care have a higher frequency of positive family history and report greater headache disability than those not consulting physicians (16). Furthermore, the pharmacological tests were performed using four different drugs and this may have reduced the possibility of highlighting statistically significant differences. Population-based studies of migraine patients may provide different results. However, we compared famM and spoM in a population that was homogeneous in terms of diagnostic criteria and disease severity. Population-based studies are often based on mailed questionnaires or telephone interviews of patients and these studies may not have the power to detect subtle clinical differences. Finally, patients with minimal headache disability are often unwilling to undergo the kind of complex psychological or pharmacological tests performed in our study.

The results of our study show that the two groups of patients examined differ significantly only in age at onset of the disease. Patients with famM have a significantly earlier (approximately 3 years) age at onset of headache attacks than patients with spoM. Despite an extensive comparison of all the other clinical, psychological and pharmacological characteristics of the disease, no additional difference was found. Our data are in accordance with a study of pediatric migraine patients that showed an earlier age at onset of headache attacks in patients with a “higher familial impact” than in those without a positive familial history of the disease (17). The most likely explanation of these results is that genetic factors play a fundamental role in setting the “migraine threshold” while environmental factors may only modify the clinical course of the disease. The findings of our study, however, do not support the hypothesis that
Table I - Demographic and clinical characteristics of patients with familial and sporadic migraine.

<table>
<thead>
<tr>
<th></th>
<th>FamM</th>
<th>SpomM</th>
<th>Tests</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients total no.</td>
<td>424</td>
<td>106</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females no.</td>
<td>324</td>
<td>82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males no.</td>
<td>100</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F/M ratio</td>
<td>3.24</td>
<td>3.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>35.73</td>
<td>38.65</td>
<td>t = 1.90</td>
<td>0.058</td>
</tr>
<tr>
<td>S.D.</td>
<td>14.14</td>
<td>14.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset of the disease (yrs) mean value</td>
<td>14</td>
<td>17</td>
<td>Mann Whitney</td>
<td>0.001</td>
</tr>
<tr>
<td>range (min-max)</td>
<td>2-47</td>
<td>5-57</td>
<td>U = 17250</td>
<td></td>
</tr>
<tr>
<td>Frequency of migraine attacks (no./year) mean value</td>
<td>48</td>
<td>36</td>
<td>Mann Whitney</td>
<td>0.212</td>
</tr>
<tr>
<td>range (min-max)</td>
<td>2-365</td>
<td>4-365</td>
<td>U = 17454</td>
<td></td>
</tr>
<tr>
<td>Duration of migraine attacks (hours) mean value</td>
<td>30</td>
<td>30</td>
<td>Mann Whitney</td>
<td>0.946</td>
</tr>
<tr>
<td>range (min-max)</td>
<td>1-192</td>
<td>3-168</td>
<td>U = 20365</td>
<td></td>
</tr>
<tr>
<td>Migraine with aura no.</td>
<td>24</td>
<td>6</td>
<td>χ² = 0.055</td>
<td>0.814</td>
</tr>
<tr>
<td>Females with aura no.</td>
<td>18</td>
<td>4</td>
<td>Fisher exact test</td>
<td>0.645</td>
</tr>
<tr>
<td>Males with aura no.</td>
<td>6</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine (with and without aura) no.</td>
<td>183</td>
<td>51</td>
<td>χ² = 0.655</td>
<td>0.418</td>
</tr>
<tr>
<td>Co-occurrence of migraine and tension type headache no.</td>
<td>241</td>
<td>55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females with co-occurrence no.</td>
<td>186</td>
<td>45</td>
<td>χ² = 0.324</td>
<td>0.569</td>
</tr>
<tr>
<td>Males with co-occurrence no.</td>
<td>55</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food-sensitive patients no.</td>
<td>169</td>
<td>35</td>
<td>χ² = 1.399</td>
<td>0.237</td>
</tr>
<tr>
<td>Non food-sensitive patients no.</td>
<td>255</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food-sensitive females no.</td>
<td>124</td>
<td>25</td>
<td>χ² = 0.001</td>
<td>0.979</td>
</tr>
<tr>
<td>Food-sensitive males no.</td>
<td>45</td>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: no. = number.

Table II - Psychological scores in patients with familial and sporadic migraine.

<table>
<thead>
<tr>
<th></th>
<th>FamM</th>
<th>SpomM</th>
<th>Tests</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI mean valve</td>
<td>9</td>
<td>9</td>
<td>Mann Whitney</td>
<td>0.841</td>
</tr>
<tr>
<td>range (min-max)</td>
<td>0-44</td>
<td>0-34</td>
<td>U=17573</td>
<td></td>
</tr>
<tr>
<td>STAI X-1 mean valve</td>
<td>38</td>
<td>40</td>
<td>Mann Whitney</td>
<td>0.121</td>
</tr>
<tr>
<td>range (min-max)</td>
<td>20-76</td>
<td>25-70</td>
<td>U = 15940</td>
<td></td>
</tr>
<tr>
<td>STAI X-2 mean valve</td>
<td>44</td>
<td>43</td>
<td>Mann Whitney</td>
<td>0.312</td>
</tr>
<tr>
<td>range (min-max)</td>
<td>22-75</td>
<td>24-68</td>
<td>U = 16572</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BDI = Beck’s Depression Inventory; STAI = State and Trait Anxiety Inventory.
famM is a different disease from spoM. On the contrary, they are in accordance with several studies which suggest that migraine is a complex disease characterized by aggregation in families due to a combination of environmental and genetic tendencies (18-20).

To our knowledge, this is the first study that has compared familial and sporadic migraine. Analysis of the phenotypic variations of clinical syndromes is important in order to verify whether a syndrome may be a distinct entity or may consist of clinically different subtypes. Such distinction is essential in performing molecular genetic studies. For example, several studies in Alzheimer’s disease (AD) have shown that patients with familial AD are clinically different from sporadic cases (21). On the contrary, no clinical difference was found between patients with familial and sporadic multiple sclerosis (22). Thus, additional clinical studies in selected pedigrees with migraine may be useful in order to support molecular genetic studies and to evaluate the heterogeneity of the disease.

Acknowledgments
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