DOI: 10.1590/0004-282X20130170

ARTICLE

Familial aggregation of cluster headache

Agregação familiar da cefaleia em salvas

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ABSTRACT

Several studies suggest a strong familial aggregation for cluster headache (CH), but so far none of them have included subjects with probable cluster headache (PCH) in accordance with the International Classification of Headache Disorders. **Objective:** To identify cases of probable cluster headache and to assess the familial aggregation of cluster headache by including these subjects. **Method:** Thirty-six patients attending a headache consultation and diagnosed with trigeminal autonomic headaches were subjected to a questionnaire-based interview. A telephone interview was also applied to all the relatives who were pointed out as possibly affected as well as to some of the remaining relatives. **Results:** Twenty-four probands fulfilled the criteria for CH or PCH; they had 142 first-degree relatives, of whom five were found to have CH or PCH, including one case of CH *sine* headache. The risk for first-degree relatives was observed to be increased by 35- to 46-fold. **Conclusion:** Our results suggest a familial aggregation of cluster headache in the Portuguese population.

Keywords: cluster headache, probable cluster headache, familial aggregation, cluster headache *sine* headache, first-degree relatives.

RESUMO

Diversos artigos sugerem uma significativa agregação familiar da cefaleia em salvas (CH) embora nenhum tenha incluído indivíduos com provável cefaleia em salvas (PCH), segundo critérios da Classificação Internacional de Cefaleias (ICHD-II). **Objetivo:** Encontrar casos de provável cefaleia em salvas e avaliar a agregação familiar da cefaleia em salvas incluindo também esses indivíduos. **Método:** Foi aplicado um questionário por telefone a 36 doentes que frequentaram uma Consulta de Cefaleias com diagnóstico de cefaleia trigémino-autonómica. Todos os familiares de primeiro grau referidos como possivelmente afetados e alguns dos restantes foram entrevistados por telefone. **Resultados:** Em 24 doentes foi diagnosticada CH ou PCH e estes tinham 142 familiares de primeiro grau, cinco dos quais foram diagnosticados como CH ou PCH, incluindo um caso de CH sem cefaleias. O risco para familiares de primeiro grau foi 35-46 vezes superior ao da população geral. **Conclusão:** Nossos resultados sugerem a existência de uma agregação familiar da cefaleia em salvas na população portuguesa.

Palavras-chave: cefaleia em salvas, provável cefaleia em salvas, agregação familiar, cefaleia em salvas sem cefaleia, familiares de primeiro grau.

Cluster headache (CH) is a form of trigeminal autonomic headache defined by a set of criteria that include a severe, unilateral pain, usually located around the orbit, combined with disautonomic manifestations affecting the same region, and usually accompanying the pain[1]. The International Classification of Headache Disorders (ICHD-II) also recognizes the concept of ***probable cluster headache*** (PCH), which requires the fulfillment of all CH criteria but one. Cases presenting with these "incomplete" forms have already been reported, and in some of these, a conversion into a "complete" form or vice-versa has occurred[2,3]. The estimate for the prevalence of CH among the general population ranges from 56 to 401 per 100.000[4-11]. A Portuguese population-based study found one individual with CH and one case of PCH among a sample of 2008 subjects[12].

Familial aggregation of this disease has been the subject of at least four studies; the results have suggested an increased risk for first-degree relatives ranging from 14- to 45-fold when compared to the general population[13-16]. These studies included only the patients and relatives fulfilling the complete set of criteria for CH.

Based on the results of this study the following hypothesis emerged: if both CH and PCH cases were included, a stronger

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Conflict of interest: There is no conflict of interest to declare.

Received 08 February 2013; Received in final form 07 June 2013; Accepted 14 June 2013.

familial aggregation could be determined. Such findings would probably contribute to strengthening the interest in finding possible genetic factors implied in the pathogenesis of this disease.

The main objectives of this study were to find cases of PCH including CH *sine* headache among relatives and to evaluate the familial aggregation of a broader spectrum of CH in a sample of the Portuguese population.

METHOD

Patient's selection

From the population evaluated in the Outpatient Headache Clinic of Hospital Santo António (Porto, Portugal) during the last 15 years, 77 consecutive and unrelated patients suspected of having a trigeminal autonomic headache were selected.

Data collection

The first step was to contact the patients in order to evaluate a structured questionnaire to allow the fulfillment of the diagnostic criteria for CH. The contact was made by telephone and during the contact the patients were asked if their first-degree relatives (parents, siblings, and offspring) have ever had a headache similar to their own or, alternatively, if their relatives have ever experienced paroxisms of disautonomic features compatible with CH, even in the absence of the headache itself. Finally, the telephone number of the first-degree relatives was requested. The second stage of this study consisted of interviewing the first-degree relatives to screen them for recurrent headaches and, in case of a positive finding, to try to match the symptoms with the diagnostic criteria for CH. The deceased relatives referred by the probands as suspects were not considered as such. Only 12 of the relatives not considered suspects were available for interview. None of the 20 interviewed relatives were observed and examined by a neurologist. Therefore, possible secondary causes for their symptoms were not excluded.

Familial aggregation

Evaluation of CH familial aggregation was based on the concept of relative risk (RR), which was calculated from the ratio between the likelihood of having an affected relative considering an affected patient, and the likelihood of having a random affected individual in the general population. The latter corresponds to the prevalence of the disease among the general population. For this purpose, the estimation obtained from a Portuguese population-based study[12] was used. RR was statistically determined using a univariate analysis for categorical variables (χ^2 test). The level of significance was set at 95% and familial aggregation was considered if the RR was greater than one.

Ethical issues

A letter containing the necessary information about this study was sent to all of the 77 patients. The Ethics Committee of Hospital Santo António approved the project.

RESULTS

It was not possible to obtain any response from 41 of the initial 77 patients due to several reasons such as death (2), refusal to collaborate (6), and incorrect contact details (33). Of the 36 subjects interviewed, 7 were excluded because their headache did not satisfy the criteria for any of the trigeminal autonomic headaches. The remaining 29 patients were classified as follows: 22 as having CH (82% with an episodic pattern and 18% with chronic CH), 2 as PCH and 5 as short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). Only the 24 patients with CH or PCH were considered in the subsequent statistical analysis. Seventy-nine percent of these patients were male (Table 1), and the mean age of onset was 34 years (standard deviation: 15,39), ranging from 11 to 70 years.

The 24 probands with CH or PCH had a total of 142 first-degree relatives. Five patients (21%) had a positive family history, with 10 possible cases among the group of relatives. Of the 142 relatives, 20 (14%) were interviewed, including 8 out of the 10 previously designated (the others had died). Three of these matched the criteria for CH and two were classified as PCH according to the ICHD-II. None of the unsuspected relatives had CH or PCH (Figure 1).

Two scenarios were considered when calculating the RR (Table 2). In the first scenario, for all the variables implied in the equation, both CH and PCH subjects were included. In the second scenario, only those individuals with CH were considered. First-degree relatives of probands with CH were estimated as having a 35- to 46-fold increased risk of having CH compared with the general population. Both values are statistically significant (p<0.05).

Cases among the affected families

The five affected relatives belonged to the families of only three probands.

One of these probands was a 58-year-old female who had an episodic CH for 15 years. She had two sisters; one aged 56 years and the other aged 61 years. The former had

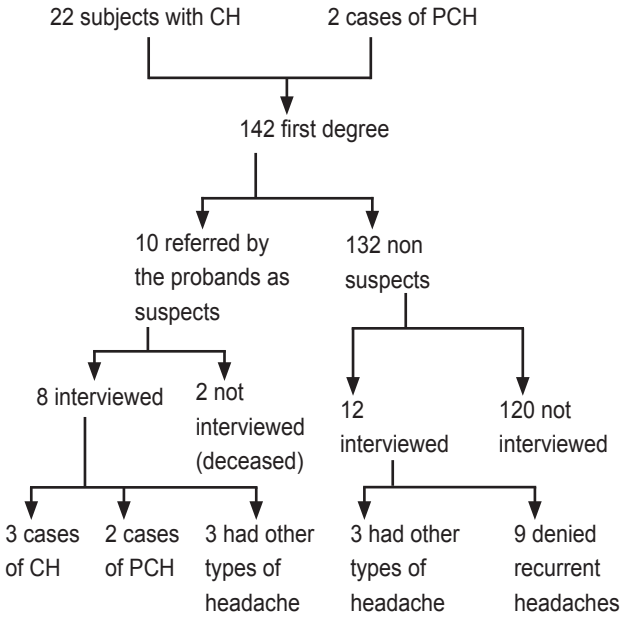
Table 1. Demographic characteristics of probands.

	Number of probands (%)	Age		Age of onset	
		Mean	Range	Mean	Range
Total	24	51	18-76	34	11-70
Male	19 (79)	49	18-76	31	11-65
Female	5 (21)	56	44-74	43	17-70

symptoms for 30 years, fulfilling all the criteria for CH except for the duration: she mentioned periods of pain lasting between 2 and 3 days. The second sister seemed to be a case of CH *sine* headache. She denied recurrent headaches, but described several episodes lasting about 30 min, during which she complained of conjunctival injection, tearing, and ptosis exclusively affecting the left eye, without any apparent precipitant. The proband mentioned that their mother displayed similar manifestations but she had already died and was not considered as an affected relative.

The second proband was a 55-year-old male describing an episodic CH. He had four siblings, including two males who also fulfilled all the criteria for CH.

The third proband, a female aged 45 years, presented an episodic CH and had a 51-year-old brother who also fulfilled all the criteria for episodic CH.



CH: cluster headache; PCH: probable cluster headache.

Figure 1. Flow chart showing probands and first-degree relatives with their clinical diagnosis.

DISCUSSION

The demographic characteristics of the patients included in this study were similar to those widely reported. The male:female ratio was found to be approximately 4:1, thus slightly higher than that described by most authors[17,18]. The age of onset is also superior to what has been reported. While most patients present their first features around the third decade of life, the probands in this study had their initial symptoms about a decade later. The findings of the two patients who began complaining of CH symptoms at an uncommon age (11 and 70 years) are noteworthy, although similar cases have been previously reported[19]. The proportion of episodic and chronic patterns of CH in this sample (approximately 4:1) is also concordant with most studies[20].

The high number of cases matching the criteria for SUNCT in this study is unexpected, as this type of headache is described as very uncommon. According to some authors, there may be some shared aspects in the physiopathology of the trigeminal autonomic headaches[21]. Furthermore, there are some case reports of successful usage of drugs like verapamil (most commonly used in CH) in patients with SUNCT[22]. While these findings may suggest some overlap between CH and SUCNT, it seems more likely that the exceedingly high number of cases in our study may be due to the origin of our sample (a tertiary headache clinic).

One of the most important aspects of familial aggregation studies is the choice of the prevalence estimation, because a small prevalence can lead to an overestimation of the relative risk and vice-versa. We used the data from a Portuguese population-based study[12] that reported one case of CH and another of PCH among 2008 individuals, thus obtaining a prevalence of approximately 50/100.000, if only CH cases are included. This estimation is similar to those obtained in the two San Marino studies[5,6] that used a thorough methodology and reported the following values: 56 and 69/100.000. Thus, the prevalence used in our study seems to be a good indicator for the prevalence of CH in southern Europe.

Table 2. Relative risk for first-degree relatives of patients with cluster headache and probable cluster headache.

		Cases included			RR	95% CI
		Prevalence	Relatives (total)	Relatives (affected)		
1st scenario	Condition	To fulfill all or all but one diagnostic criteria	Should be related to a proband who fulfills all or all but one diagnostic criteria	To fulfill all or all but one diagnostic criteria	35.21[a]	14.56–85.14
	Value	1:1000	142	5		
2nd scenario	Condition	To fulfill all the diagnostic criteria	Should be related to a proband who fulfills all the criteria	To fulfill all the diagnostic criteria	46.15[a]	14.58–146.09
	Value	0.5/1000	130	3		

RR: relative risk; CI: confidence interval.
[a] For both RR values, $p<0.05$.

Considering the reports of cases presenting with PCH that later developed a CH[3] or vice-versa[2], as well as the suggestion of a broader clinical spectrum for CH, it seemed appropriate to include individuals who present with PCH, and not just CH, in epidemiological studies. In our first scenario we obtained a RR of 35 and for the second a 46-fold increased risk for first-degree relatives. The difference between both values may be partially explained by the lower prevalence used in the second scenario. Thus, the hypothesis of a higher RR with the inclusion of PCH subjects was not confirmed.

The previous four published familial aggregation studies reported an increased risk for first-degree relatives ranging from approximately 14- to 45-fold[13-16].

Both Russell et al.[13], in Denmark, and Leone et al.[14], in Italy, used a similar methodology and determined a RR of 14.1 and 39, respectively, for first-degree relatives. We can identify at least four important differences when comparing these studies with ours. Firstly, in these studies, only the possibly affected relatives were interviewed. Another difference has to do with the non-inclusion of PCH subjects. Furthermore, they included deceased relatives as long as the description provided by the probands was detailed enough to classify them according to ICHD. Finally, the prevalence used in these studies (69/100.000) was only slightly higher than the one considered for our equivalent scenario (50/100.000). The samples used by these authors were far larger than ours and the confidence intervals were considerably narrower, giving an important consistency to their results.

In France, El Amrani et al.[15] introduced what seems to be a methodological advantage: all first-degree relatives were directly interviewed by a neurologist. In the other studies, including ours, some affected relatives may have been lost because of a possible underreporting by the probands.

Kudrow and Kudrow[16], with a North-American sample, found a RR of 45. However, the family history provided by the probands was not confirmed by a direct interview with the relatives, which may have led to an overestimation of RR.

The most important limitation of our study is the small number of subjects included, which withdraws some consistency to our results, especially when compared with similar studies. Furthermore, our sample was collected from a tertiary center, and thus a direct extrapolation for the general population cannot be done.

Only a small proportion (14%) of the first-degree relatives was interviewed in this study and the remaining relatives were considered to be unaffected (according to the information provided by the probands). However, taking into account the possibility that there could have been some affected relatives among those not interviewed, their inclusion in the equation would have resulted in an even greater RR. Also, if this calculation was made using only the relatives who were interviewed, the RR value would have been higher. Thus, this limitation may have lead to an underestimation of the RR in this study.

Telephonic interviews have been described as a valid instrument in familial aggregation studies and prevalence studies[23,24], particularly because they allow the clarification of difficult or ambiguous questions. So the use of telephone interviews seems to be an important advantage of our study. Another positive aspect is the use of a prevalence estimation obtained from a similar population.

Finally, to the best of our knowledge, our study is the first one that includes individuals with PCH, which seems to be a major advantage given the reports of a broader spectrum for the disease. Although we have not confirmed a greater RR with this addition, our results provide significant evidence of a strong familial aggregation, thus reinforcing the theory of a genetic basis for CH. In the future, a larger study with a similar methodology may be important to support these results.

Acknowledgments

The authors would like to thank Dr. Ângela Timóteo and Dr. José Barros for reviewing the manuscript and for their suggestions.

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