Report of cluster headache in a pair of monozygous twins

Abstract A pair of identical twins with cluster headache is described. Monozygosity was confirmed by the identification of 14 DNA markers. In spite of harboring the same genes, the clinical picture presented by the twins was not exactly the same. Cluster headache is probably the best known trigeminal-autonomic cephalalgia, but several questions regarding its pathophysiology remain to be answered. The cases described herein reinforce the role of genetic aspects in its etiology.

Key words Cluster headache • Genetic aspects • Monozygous twins • Trigeminal-autonomic cephalalgias • Twins

Introduction

Cluster headache is characterized by unilateral excruciating head pain, associated with autonomic phenomena and circannual periodicity [1]. In the general population, its prevalence is thought to be 69 per 100 000 persons, affecting mainly males [2]. Although there is evidence of a hypothalamic dysfunction in the pathogenesis of cluster headache [3], its occurrence with an autosomal dominant pattern of inheritance in some families [4], the higher risk described in relatives of patients with this condition [4–6] and its previous occurrence in identical twins [7–11] suggest a genetic basis. We report a pair of monozygous twins presenting cluster headache. Monozygosity was confirmed by 100% concordance of alleles in 14 loci. Our data add to the existing literature, and reinforce the view that genes for cluster headache should be searched for.

Case reports

Two 45-year-old male twins (Table 1) had unquestionable cluster headache according to criteria of the International Headache Society (IHS) [1]. None had previously
submitted to proper prophylactic or acute therapy. Both differed with respect not only to the characteristics of their headaches, but also with regard to the associated conditions and environmental aspects. One of them (twin #2) experimented a four-year remission after a conversion to the evangelical faith. There was neither family history for cluster headache nor parental consanguinity. Their only sister had migraine without aura (Fig. 1).

After the approval of the local ethics committee had been obtained, as well as signed informed consent from the patients, the homozygosity of the twins was tested by PCR-STR for the following loci: D3S1358, HumvWA, HumFIBRA, D8S1179, D21S11, D5S818, D13S317, D7S820, D16S539, TH01, TPOX, CSF1PO and amelogenin [12]. All tested loci showed the same genotype for both patients, as expected for monozygous twins.

### Discussion

Both cases of cluster headache were diagnosed according to the IHS criteria [1]. Their clinical features did not differ from those previously described in the literature. Smoking is a common finding in cluster headache patients [8, 9] and the partial response to enalapril is anecdotal and may mirror that which has been reported for angiotensin converting enzyme inhibitors for migraine [13]. Patient #2’s transient remission after a religious conversion may reflect a psychosomatic influence on the behavior of headaches. Paroxysmal tachycardia as reported by Sjaastad et al. [10] in a pair of twins was not observed. A striking aspect is the difference in the clinical presentation between the twins. Variations in the manifestations of cluster headache in twins have been described in previous reports [8–11], as well as in other disorders occurring in monozygous twins. These variations have been attributed to the timing of twinning, to antenatal environmental fac-

### Table 1 Clinical findings in two 45-year-old male twins with cluster headache (CH)

|                      | Twin # 1                                      | Twin # 2                                      |
|----------------------|----------------------------------------------|----------------------------------------------|
| Age at CH onset, years | 17                                           | 8 (single attack), recurring at the age of 17 |
| Site and side of pain | Eye and ipsilateral temple, radiating to the occipital area and alternating at each cluster period | Left temple                                   |
| Duration of pain     | 2–3 hours                                    | 50 minutes                                   |
| Episodes/day          | 1–2                                          | 3                                            |
| Circadian pattern     | Erratic or after meals                       | Fixed but different at each cluster period   |
| Circannual pattern    | Jul–Aug, Feb–Mar                             | Feb–Mar, Jun–Jul, Aug–Sep                    |
| Cluster periods/year  | 2                                            | 4                                            |
| Length of cluster periods | 1.5–2 months                               | 1–1.5 months                                 |
| Autonomic phenomena   | Ipsilateral                                  | Ipsilateral                                  |
| Trigger factorsa      | Alcohol                                      | –                                            |
| Relieving maneuvers   | Exercise                                     | Alcohol inhalation, local cooling            |
| Associated conditions | Smoking, hypertension, hemorrhoids           | Smoking, hypertension, obesity, alcoholism (in remission) |

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Fig. 1 Heredogram of the cluster headache twins. ■, cluster headache; ●, migraine without aura.
tors and to several genetic mechanisms, such as DNA mutation, epigenetic modification (promoter region methylation), or changes in number and morphology of chromosomes at a karyotype level. Additionally, there are some differences of unknown origin [14].

Although not recognized as a purely genetic disorder, the occurrence of this type of headache in two individuals with the same genotype reinforces the role of the genetic aspects. Previous reports on identical twins with cluster headache were based on phenotype similarity [7–10] or on a comparison of blood groups [8, 10], HLA haplotypes [8–11], and DNA markers [11].

Eventually, an autosomal dominant pattern may occur in some families [4]. In a series of 421 cluster headache individuals in Denmark, Russel [4, 5] found that first-degree relatives had a risk of developing cluster headache 14-times higher than the normal population. Kudrow and Kudrow [6] noted a genetic link with migraine. A genetic basis for migraine, another trigeminovascular cephalalgia, seems unquestionable [19].

May et al. [3] described a hypothalamic involvement in the genesis of cluster headache. The involvement of specific HLA haplotypes in cluster headache has not been confirmed to be consistent [22, 23], in spite of early reports of a reduced frequency of the HLA B14 antigen [24]. The cases herein described add to the existing evidence of a genetic influence on the genesis of cluster headache. The scientific community would welcome efforts in the search for such genes.

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