Abstract Basilar-type migraine (BM) and hemiplegic migraine are clinically distinct subtypes of migraine with aura, however they do share clinical features and it is possible they may share genetic bases. In recent years, \textit{ATP1A2} and other gene mutations have been discovered in familial and sporadic hemiplegic migraine. More recently, an \textit{ATP1A2} mutation has been identified in an Italian family with BM. In this study we document the absence of \textit{ATP1A2} mutations in two Italian sisters with menstrual BM, suggesting that other genes are involved in the condition.

Keywords Basilar-type migraine · \textit{ATP1A2} gene · Menstrual migraine

Introduction

Migraine is a complex debilitating primary neurovascular headache affecting 15% of western populations. According to ICHD-II [1] diagnostic criteria, there are six major types of migraine, the two most important being migraine without aura and migraine with aura. Basilar-type migraine (BM), familial hemiplegic migraine (FHM) and sporadic hemiplegic migraine (SHM) are considered subtypes of migraine with aura, although they differ clinically and genetically. The last few years have seen rapid advances in our understanding of the genetics and molecular biology of migraine with the identification of the FHM1 (\textit{CACNA1A}) [2], FHM2 (\textit{ATP1A2}) [3] and FHM3 (\textit{SCN1A}) [4] genes.

Recently, a novel mutation (R548H) found at the FHM2 locus on the \textit{ATP1A2} gene was documented in an Italian family with BM suggesting that this migraine subtype and FHM might be allelic disorders [5]. We report on two Italian sisters with BM who do not harbour this mutation in the \textit{ATP1A2} gene.

Case reports

Clinical features

Two sisters, 32 and 38 years old, presented at the Headache Center of Avellino (Campania, Italy) for the first time two years ago with migraine attacks fulfilling ICHD-II criteria for BM. No attacks of migraine with aura...
without basilar-type symptoms occurred in either patient. No other relative presented headache or headache history.

The younger sister, a housewife, reported a history of BM attacks following a closed brain injury at age 13. She suffered no other relevant medical condition. A typical BM attack was characterised by slowly worsening bilateral blindness, and bilateral hand paraesthesia spreading to the mouth and tongue, developing over about five minutes. Ten to 15 minutes after the onset of these symptoms, a severe dull headache developed, located in the bilateral forehead. The pain was accompanied by nausea, vomiting, photophobia and phonophobia and lasted 5–6 h, despite treatment with NSAIDs. No drugs were taken before BM attacks (premenstrual symptoms or migrainous premonitory symptoms).

Over the previous 10 years the headaches had occurred about once a month, generally on the day proceeding menses. Two months before coming to our initial observation, she stopped taking the oral contraceptives that she been on for the previous 6 years and experienced a six-month period without headaches. The BM attacks then reappeared at reduced frequency and pain intensity, still in association with menses. She recalled that complete remission of BM attacks had occurred for the duration of previous pregnancies. She was not taking any medication at the time of observation. She reported that her older sister experienced similar headache attacks.

The older sister reported sporadic episodes of syncope of unknown aetiology during childhood, and headache attacks with BM features from age 16. A typical attack was characterised by slowly worsening bilateral blindness, bilateral hand paraesthesia spreading to the mouth, and speech disturbances. These symptoms lasted no more than 20 min and when they had disappeared, right unilateral severe dull pain began, which lasted 12–24 h. The pain was exacerbated by physical activity and accompanied by nausea, photophobia, phonophobia and light-headedness. No drugs for premenstrual symptoms or pain killers were ever taken. Attacks occurred about once a month and always began on the day preceding menstruation. She had taken oral contraceptives for about a year in the past but there had been no change in the frequency of attacks. However the attacks disappeared during pregnancy. Neurological and psychiatric examinations were normal in both patients. Biochemical analyses, ophthalmological examination, echo-colour Doppler of the supra-aortic vessels, standard EEG, gadolinium-enhanced brain MRI and angio-MRI in both women revealed nothing remarkable. Cerebral SPECT during a headache-free period (two months after the latest attack) did not reveal perfusional changes in either patient. Since the younger sister occasionally had dyspnoea exacerbated by mild effort, she underwent more extensive cardiological evaluation. Only in this patient transoesophageal echocardioccolour Doppler revealed aneurism of the fossa ovale without a patent foramen ovale or shunt.

Both patients started on lamotrigine to a maximum of 100 mg/day. After more than a year of follow-up they remained free of BM attacks.

Genetic study

The genetic study was performed after written informed consent and approval of the local ethics committee. Genomic DNA was extracted from peripheral venous blood leukocytes by standard procedures.

Exons 4, 13–17, 25–27 and 32–37 of the CACNA1A gene and exon 23 of the SCN1A gene, all known to carry mutations associated with FHM and SHM, were analysed by direct sequencing. Each PCR amplicon was designed with oligo 4 software and included intron/exon boundaries.

Approximately 50 ng of DNA from each patient was added to a mixture containing 0.5 μM of each primer, 1X PCR buffer (Invitrogen), 0.2 mM of each dNTP (Amersham), 1.5mM MgCl2, and 0.5 U Taq DNA polymerase (Invitrogen) in a reaction volume of 25 μl. Conditions were denaturation at 94°C 3 min, followed by 35 cycles at 94°C for 30 s, MT for 30 s and 72°C for 45 s, followed by 72°C for 10 min. PCR fragments were purified with ExoSAP-IT (Amersham) and sequenced with the BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems, Warrington, UK) according to the manufacturer’s instructions using a 9700 Thermal Cycler (Applied Biosystems). The fluorescent labelled fragments were run on the ABI Prism 3100 Genetic Analyzer (Applied Biosystems). Polymorphisms were detected by multiple alignments of sequences, using the Autoassembler software (Applied Biosystems). No mutation was found.

We then sequenced all 23 coding exons of the ATP1A2 gene, using 14 sets of primers each located at least 60 nucleotides from exon–intron boundaries (sequences available on request). PCR and sequencing reactions were performed as described above.

The analysis failed to identify any mutation in the ATP1A2 gene in either patient.

However, we detected, in homozygosis, in both patients, two known [6] intronic polymorphisms (intron 1 c.13-7_13-8 insTCCT and intron 5 c.495+65C>T).

Discussion

BM and hemiplegic migraine are clinically distinct subtypes of migraine with aura. Mutations in the ATP1A2 gene have been reported in FHM [2, 3, 6] and more recently in an Italian family with five members suffering from BM [5]. This finding provided the rationale to search for ATP1A2 mutations in our Italian probands, even though a distinct pattern of BM attacks was not reported in the Italian family. We focused our attention on ATP1A2 because to date only this