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BRIEF REPORT

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A case of MELAS syndrome with typical cluster headache attacks: is it a causal or coincindental association?

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Abstract Many findings relate migraine and cluster headaches to a genetic alteration, even if the site of the defect has not been identified. Some of these findings indicate an involvement of mitochondrial DNA, although some contrasting results have been reported. We describe a case of cluster headache occurring in a patient with MELAS syndrome. The diagnosis of MELAS was supported by the familiar anamnesis (the mother suffered from a similar form), by the laboratory reports (lacto-acidosis), by instrumental analysis (signs of encephalopathy on magnetic resonance imaging) and by biopsy findings (myopathy). The diagnosis was confirmed when a point mutation (Leu mutation at position 3423 of mitochondrial RNA) was found in the mitochondrial gene. The recurrent periods, characterized by attacks of unilateral pain and accompanied by homolateral symptoms (e.g. tearing, palpebral ptosis, rhinorrea), did not leave any doubt as to the diagnosis of cluster headache. We discuss whether the co-existence of MELAS and cluster headache was coincidental or causal.

Key words Cluster headache • mtDNA • Lacto-acidosis • MELAS • Mitochondrial disease

Introduction

MELAS, a syndrome characterized by myopathy, encephalopathy, lactic acidosis and stroke-like episodes, has been related to an alteration in mitochondrial DNA (mtDNA). Mitochondria are intracellular organelles which are the sites of the oxidative phases of cell respiration [1]. Mitochondria have their own DNA. In most eukaryotes, mtDNA exists as a double-stranded, closed circle which has the capability to replicate. Mitochondrial genes have been identified to code 13 proteins that are essential to the cellular respiratory functions of the mitochondria [2]. Protein encoded by intra-organelle genes act, along with proteins of nuclear origin, to guarantee the respiratory function of the mitochondria. Because cellular respiration is such an intricate metabolic process, disruption of any mitochondrial or nuclear gene by mutation is likely to have impact on that organism. mtDNA is particular vulnerable to mutations [3]. The inheritance of mitochondria-related diseases is more complex than that of diseases due to genetic alterations of the nucleus. A zygote receives a large number of organelles through the egg. Only few of them contain a mutation. During the early phases of life, cell division disperses the initial population of the mitochondria and new populations of the organelles are reproduced by the original. Therefore, if a mutation is present in some of the initial populations of mitochondria, the adult cell will have a variety of organelles, both normal and abnormal. This condition is called heteroplasmy [4].

Human disorders that are attributable to mutations of the mtDNA have to meet several criteria. They can be either

sporadic, when mutations occur in somatic cells, or inherited when the gene alteration is present in oocytic organelles. Inheritance must exhibit a maternal rather than a mendelian pattern. The mtDNA alteration must produce a deficit in the bio-energetic function of the organelle [5]. On the other hand, a disruption of mitochondrial function could also arise from a nuclear gene alteration. Mitochondrial disorders can be categorized as due to: primary mutations of DNA, either sporadic or maternally inherited; nuclear mutations which provoke either direct alterations in mtDNA or intergenomic signalling defects; mendelian defects that affect the respiratory chain in the absence of mtDNA mutations. The difference (if one exists) in the pathophysiology of these three possibilities has not been determined [6].

MELAS is one of the major mitochondria-related encephalomyopathies. MELAS has been related to a point mutation resulting in the presence of leucine in position 3234 of mitochondrial tRNA [7].

MELAS has been related to migraine, in as much as the symptomatology is often characterized by migraine-like attacks (i.e. headache with nausea and vomiting). The relationship between MELAS and migraine-like attacks and the consideration that migraine could have a familiar inheritance with a preferential maternal line have suggested possible common elements at the basis of the two clinical entities [8]. One study showed that there was a high frequency of mitochondrial gene alterations (same Leu mutation) in a population of migraine patients [9]. These findings were not confirmed by a subsequent investigation [10], nor was an alteration in mtRNA found in cluster headache patients [11]. On the other hand Montagna [12] demonstrated, with spectroscopy resonance, an alteration of the neuronal cell respiratory function in cluster headache patients, while Montagna et al. [13] described a case of cluster headache with an extensive deletion of the mitochondrial genome. These findings support the hypothesis of the hereditability of migraine and cluster headache. We described a case of a typical cluster headache feature in a subject with MELAS.

Case report

A 37-year-old man came to our observation at the headache centre of Rome. He reported episodes of headache which occurred over a period of about 2 months. These periods reoccurred with a frequency of twice a year for 7 years. During these periods the occurrence of the headache attacks had an impressive chronological pattern: the attacks occurred every day at 1:00 a.m. and 4:00 p.m. Each attack lasted about 45 minutes. The pain was localized in the left side, involved the orbit and the facial and parietal regions, and spread to the maxillary area. Pain was described as excruciatingly sharp. Accompanying symptoms usually described for cluster headache occurred, along with other (stroke-like) symptoms not usually associated. In particular, conjunctival hyperemia, tearing, palpebral ptosis, and nasal obstruction were always present on the same side as the pain. These episodes matched the diagnostic crteria outlined by the Ad Hoc Committee of the International Headache Society (IHS). In addition, hemiplegia, aphasia, and blindness often occurred during the crises, and disappeared at the end of the attacks. He reported that his mother suffered from an analogous form, with cluster headache-like attacks (even if the pain intensity was described as significantly lighter) accompanied by the same stroke-like symptoms (hemiplegia, aphasia, amaurosis). It was not possible to evaluate if other analogous cases occurred in his pedigree

The personal anamnesis showed that before the occurrence of the cluster period, the patient had suffered from stroke-like attacks that had the same duration as that of the accompanying headache. The chronological pattern of these pre-cluster episodes was not determined, occurring 5–6 times during a year. No other important pathologies were referred. The stroke-like attacks which occurred before the onset of the cluster headache-like disease were similar to those present during the headache attacks. The patient referred transitory (5–10 min) episodes of amaurosis, with loss of coordination, hemiplegia and, sometimes, aphasia.

The general clinical investigation revealed a light hypotrophy of the muscles with relative weakness. Neurological examination was normal. Neuroimaging techniques documented the presence of encephalopathy, particularly at the posterior level (Fig. 1). No lesions were found in the hypothalamus. Electromyographic examination demonstrated the myopathic alteration. Laboratory investigation did not reveal any abnormal values. A significant increase of lactic acid in the blood was found during the attacks. The basal values were 15 mg/dl 2 hours after the crisis. They increased to 80–110 mg/dl during the crisis, and descended to 20 mg/dl at the end of the crisis Electrocardiographic features were not altered. A muscular biopsy was carried out in order to examine the mtDNA along with the leucocytic mtDNA. The polymerase chain reaction (PCR) technique was applied to sequence the DNA. A point mutation was found (cytosine to thymine). The mutation was related to the Leu alteration in the tRNA at position 3243.

The last cluster headache-like period was treated with verapamil (oral dose of 80 mg, 3 times a day), which appeared to shorten the length of the florid phase (40 days). The attacks were treated with oxygen, which only partially (30% as reported by the patient) attenuated the intensity of the attack, whereas the duration was unaffected.

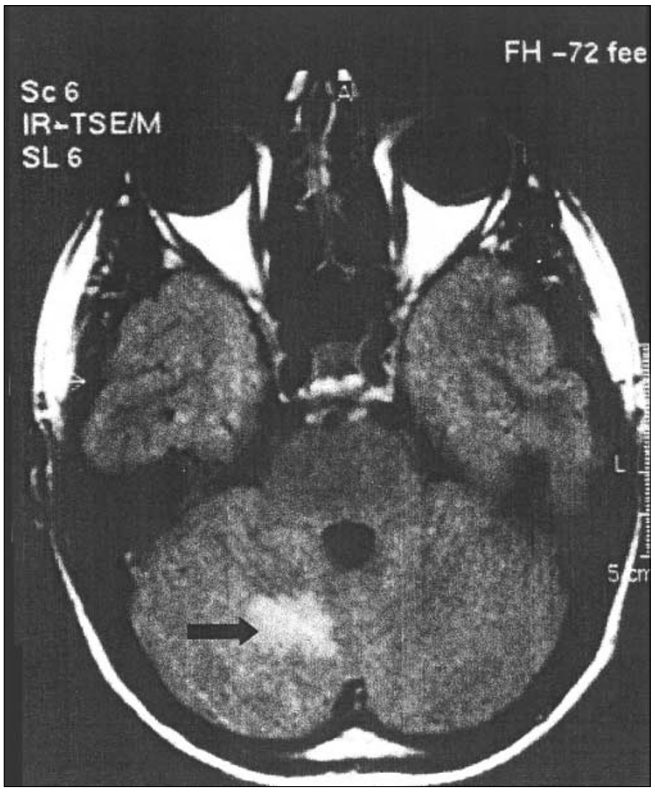

Fig. 1 MR image showing an ischemic-like lesion at the cerebellar level (*arrow*)

Discussion

We described a patient with typical cluster headache attacks co-existing with stroke-like symptomatology. The attacks were also characterized by an increase in lactic acid well above the normal level. The instrumental investigation indicated the presence of encephalopathy and myopathy. The patient's mother was affected by an analogous form of headache. The presence of a point mutation in the mtDNA confirmed the diagnosis of MELAS, with a possible maternal inheritance. MELAS is often characterized by migraine-like attacks, and this had encouraged studies on the possible involvement of mtDNA in migraine. The only study which described an elevated frequency of mitochondrial alterations was not confirmed by others which have followed. A survey carried out on cluster headache patients showed that their mtDNA was normal. Thus, an alteration of mtDNA in the common pathogenesis of migraine and cluster headache was excluded. On the other hand, evidence that the syndromes characterized by altered mtDNA could sometimes show migraine or cluster headache-like characteristics indicates that a dysfunction of the mitochondria could contribute to the headache attacks. Our case is significant in this sense, as it occurred in a patient who has features of MELAS syndrome with typical cluster headache attacks. The high blood level of lactic acid observed only during the headache attacks is suggestive of an involvement of acidosis in the genesis of cluster headache. Acidosis could participate in the pathogenesis of cluster headache at either a peripheral or central level. Peripherally, a decrease in pH could stimulate the nociceptive fibers that are putatively involved in genesis the cluster headache attacks. The proton (H^+) is a potent activating stimulus of nocicpetive fibers. On the other hand, metabolic acidosis could interfere with central nervous system function, in this case by evidentiating a hypothetical alteration of some central structures.

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