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Neurophybromatosis type 1 and vascular risk: outlining a new hypothesis

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Abstract

Background: The neurofibromatosis of type 1 (Von Recklinghausen disease) -NF1- belongs to the genetic disorder group known as phakomatosis. Its inheritance pattern is dominant autosomal with variable penetrance. It is produced by the mutation of the gene NF1 of the chromosome 17q (tumour supresor gene which encodes a protein -neurofibromine- which modules the transduction of signals through the guanosin triphosphatase path -GTPase-). It's characterized by the presence of benign tumors from the peripheral nerves which are nominated neurophybromas (they are compounded by the proliferation of Schwann cells and phybroblasts), pigmented skin lesions ("café au lait spots"), freckles on unexposed areas like the armpits, iris hamartomal (Lisch's nodules) and seudoarthrosis of the tibia [1, 2]. It has been described that the patients with NF1 can present neurovascular abnormalities which tend to brain ischemia [3], although this uncommon association is not well characterized.

Case report

We present a 74 year-old male case, with moderate intelecta deficit referred since his childhood, which presented grade II hypertension and dyslipidemia presedents correctly treated. There were previous episodes of ischemic cerebrovascular disease, the first one, 8 years before the current entrance into the posterior cerebral artery territory, after which an antiplatelet treatment with 300 mg/d of acetylsalicylic acid -ASA- was prescribed; the second one 5 years after, in the left half brain artery territory, with residual mild right paresis, after which a therapy with 75 mg/d of clopidogrel and 100 mg/d of ASA was combined. He also performed ophthalmology controls by compatible findings with ischemic optic neuritis in the right eye. He enters in our Departament with dyspnea and stupor in relation with infection of respiratory tract. Frontal macrocephaly was aimed to on physical examination and they were striking pigmented lesions in armpits and groins, as well as multiple cutáneos tumors of predominance in lumbosacral region; there was right hemiparesis IV/V and ipsilateral palpebral ptosis. Neutrophilic leukocytosis highlighted in complementary exams it (12800 leukocytes per microliter with 95 % of neutrophils), as well as an elevation of severe phase reactants, with eritrocitic sedimentatoin rate (ESR) of 64 mm/h and protein C reactive (PCR) of 3.4 mg/dl, secondary findings to its infectious process in course; the anticardiolipin antibodies were negative. The thoracic radiology revealed a laminar atelectasis bases right lung. A cerebral neuroimaging study was performed by magnetic resonance which described multiple punctiform ischemic lesions in protuberance and bulbous-pontine junction, internal capsules, corona radiata and left thalamus.

The referred learning difficulties, as well as the phenotypical characteristics of macrocephaly, freckles in armpits and cutaneous tumors indicated a possible neurocutaneous syndrome therefore a cutaneous biopsy was requested which confirmed the suspicion of neurophybromas and a genetic study documented NF1 gene mutation of the 17 chromosome. Due to the reiteration of the cerebral ischemia pathology (3 episodes in less than a decade) despite a correct treatment of changeable cardiovascular risk factors and after discarding a an-

tiphospholipid syndrome and others thrombophilic disorders (Leyden V factor, protein C and S deficit, antithrombin III, prothrombin mutation,…), the MTHFR gene was requested which reflected a mutation of itself.

Discussion

It is well know that determined congenital defects such as NF1 lead to a more frecuently thrombotic phenomenon production and at an earlier age that in the general population, reporting in a serie of 69 patients with NF1 a 7,2 % of stroke at a lower age at 50 years old [4]. In this pathology, cerebral vessels can present cervicofacial arterial dysplasia, single or multiple cerebral aneurysm [5], arteriovenous fistula and stenosis or great or small caliber vessels occlusion, even it is associated to the Moyamoya's disease [6. 7]. The microscopic examination of the affected arteries reveled a concentric proliferation of the smooth muscle cells of the intima, the medial layer and/or fragmentation of the internal elastic sheet, being able to interest to any vessels of any caliber, predisposing to cerebral ischemia at any age that would be enhance by the coexistence of other vascular risk factors, therefore its strict control should be a priority to these patients [8].

In this patient, when repetition thrombotic phenomenon occurs, after successful correction of midifiable vascular risk factors and double antiplatelet therapy, one may suspect a possible underlying genetic disorder which was confirmed after with MTHFR (metilen tetrahydropholate reductase) gene genetic studies.

The homocysteine is a vital importance aminoacid in cellular metabolism. It is metabolized by transulfuration to cistationine or for remetilation to metionine. Deficiency in enzymes that catalize homocysteine other in the enzymes that catalize the transulfuration and the remetilation produce a homocysteine accumulation. The MTHFR enzyme plays a key role in this remethylation path which needs vitamin B12 as substratum. It is very important the cystathionine-b-synthetase in the transulfuration path [9]. Hyperhomocysteinemia is produced when the homocystein metabolism is decreased and it is considered as atherogenic factor in cardiovascular diseases and above cerebrovascular diseases. In the last years, the relation between hyperhomocysteinemia and neuronal damage has been highlighted through several neurotoxicity mechanisms as [10]: oxygen reactiv species generation, prothrombotic effects, oxidative stress promotion, homocystein derivates formation (tiolactone which is combined with LDL-cholesterol inducing atherosclerotic plaque development), beta-amiloide protein toxicity increased and apoptosis activation. The cerebral microvasculature alterations associated to prothrombotic alteration which conditions the hyperhomocisteinemia, could nullify great part of the antithrombotic and antiatherogenic effects of antiplatelets drugs and statin conditioning a neuroprotection absence despite an adecuated administration of the same things, being the first case of such characteristics described in the literature. We propose the fulfilment of MTHFR mutation screening studies in patients with NF1 and in case the same documented itself, to assess folic acid treatment.

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