Clinical Neurology and Neurosurgery 114 (2012) 758–761

Contents lists available at SciVerse ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Case report

Clinical, neuroradiological and molecular features of a patient affected by pseudoxhantoma elasticum associated to carotid *rete mirabile*: Case report

Elisabetta Del Zotto[a,*], Marco Ritelli[b], Alessandro Pezzini[a], Bruno Drera[b], Massimo Gamba[c], Alessia Giossi[a], Irene Volonghi[a], Paolo Costa[a], Sergio Barlati[b], Roberto Gasparotti[d], Alessandro Padovani[a], Marina Colombi[b]

[a] *Clinica Neurologica, Dipartimento di Scienze Mediche e Chirurgiche, Università degli Studi di Brescia, Brescia, Italy*
[b] *Sezione di Biologia e Genetica, Dipartimento di Scienze Biomediche e Biotecnologie, Università degli Studi di Brescia, Brescia, Italy*
[c] *Neurologia Vascolare, Stroke Unit, Spedali Civili di Brescia, Brescia, Italy*
[d] *Neuroradiologia, Dipartimento di Diagnostica per Immagini, Università degli Studi di Brescia, Brescia, Italy*

ARTICLE INFO

Article history:
Received 17 August 2011
Received in revised form 6 December 2011
Accepted 20 December 2011
Available online 23 January 2012

Keywords:
Cerebral infarct
Pseudoxanthoma elasticum
Carotid rete mirabile
Connective tissue disorders

1. Introduction

Pseudoxanthoma elasticum (PXE) is an autosomal-recessive disorder of soft connective tissue primarily involving eyes, skin and vascular system.

A progressive fragmentation and calcification of internal elastic layer leads to a secondary thickening of the intima and disruption of the arterial architecture, which commonly resembles a premature atherosclerosis. Ischemic stroke is the most frequently reported neurovascular manifestation of PXE either as a direct consequence of the arterial narrowing or secondary to the high incidence of associated hypertension, which acts as accelerating factor [1].

Carotid *rete mirabile* (CRM) is an abnormal collateral pathways of braided, freely anastomosing vessels, between the internal carotid artery (ICA) and the external carotid artery (ECA), mainly branches of the maxillary artery, typically located around the cavernous sinus. CRM represents a physiological anatomical structure in lower vertebrates, while it has been rarely shown in humans either with hemorrhagic or with ischemic manifestations. To date, only 37 cases of CRM have been reported in humans, 4 of which affected by PXE [2–5]. Therefore, the relation between these two condition is uncertain.

2. Case report

A 39-year old woman was admitted for sudden onset of left facial-brachial paresthesia, mild hypostenia of the left arm and headache. She was current smoker but no other vascular risk factors, including migraine and family history of cardiovascular disease were detected.

A clinical diagnosis of PXE was made based on the presence of typical yellowish cobblestone-like skin lesions on the neck and of angioid streaks in both *fundi* on ophthalmological examination. Fluorescein angiography and histopathologic analysis of a skin biopsy sample showing calcification of the dermal elastic fibers supported the diagnosis.

Following informed written consent from the patient, molecular analysis of *ABCC6* gene (Ref. seq. NM_001171.2) was performed. In particular, the 31 exons and intron/exon flanking regions of *ABCC6* gene were amplified by PCR and sequence analysis was performed in both orientations, disclosing the recurrent c.1995delG microdeletion in exon 16, leading to frame-shift and PTC, and the novel c.794 + 1G > A transition, affecting the donor splice-site of intron 7 (Fig. 1 A). To verify the effect of this splice mutation, RT-PCR

* Corresponding author at: Clinica Neurologica, Università degli Studi di Brescia, P.le Spedali Civili, 1, 25100 Brescia, Italy. Tel.: +39 030 399 5631 5632; fax: +39 030 399 5027.
E-mail address: betty.delzotto@tin.it (E. Del Zotto).

0303-8467/$ – see front matter
doi:10.1016/j.clineuro.2011.12.031

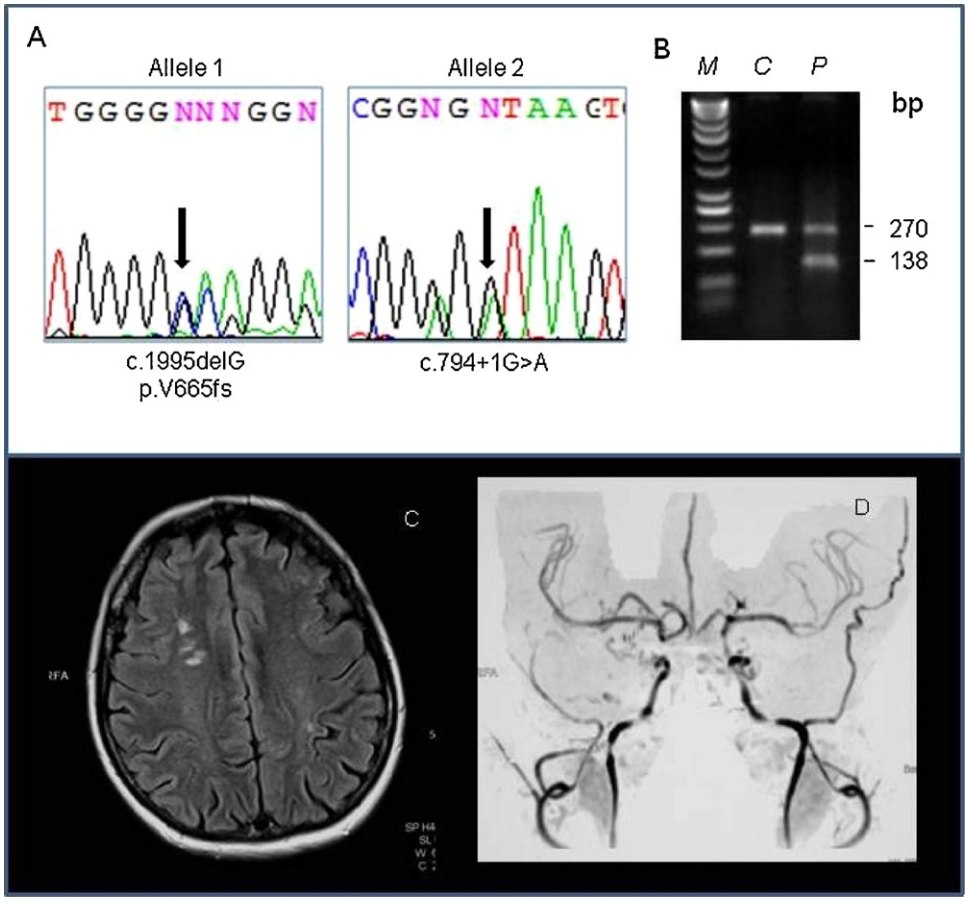

Fig. 1. Disclosed mutations in sequence analysis of the *ABCC6* coding region (A). The c.794 + 1 G > A mutation leads to in-frame skipping of exon 7: agarose gel electrophoresis of cDNA, amplified with primers encompassing exons 6–8, shows in the patient (*P*), in addition to the expected fragment of 270 bp seen in the control (*C*), the presence of a 138 bp aberrant band, lacking exon 7 (B). Magnetic Resonance, Axial Flair section (C), MRA, coronal MIP view (D).

was performed: amplification of the cDNA region covering exons 6–8 demonstrated in-frame skipping of exon 7 (Fig. 1 B), leading to the deletion of 44 amino acids in the third cytoplasmic domain of the protein.

Brain MRI showed multiple watershed ischemic lesions in the right frontal white matter (Fig. 1C). MR Angiography revealed poor visualization of the carotid siphon with intact A1 and M1 segments and a hypertrophied left middle meningeal artery (Fig. 1 D).

Digital subtraction cerebral angiography demonstrated bilateral segmental agenesis of the C5 and C6 segments of the carotid siphon with development of a *rete mirabile* network, which represented a collateral circulation through hypertrophied infero-lateral and meningo-hypophiseal trunks responsible for the recanalization of the ophthalmic and supraclinoid segments of the ICA (Fig. 2A–D). The ICA diameter was markedly diminished bilaterally. M1 and A1 segments were not involved. Dural-pial collateral vessels from the ECA through the left middle meningeal artery were also detected (Fig. 2 E). Posterior circulation was intact (Fig. 2 F).

Aspirin at low dosage (75 mg/die) was started. During a follow-up period of 10 years, the patient did not experience bleeding complications or recurrent cerebral ischemic events.

3. Discussion

In young PXE patients the relative risk of ischemic stroke has been estimated at 3,6%, mainly referable to small vessel occlusive disease [1]. In our case, the multiple ischemic subcortical lesions seem to be related to insufficient flow to distal areas, although a small vessel involvement can not be ruled out a priori.

Besides the location and the degree of arterial involvement, vascular manifestations in PXE may be conditioned by vascular collateral pathways brought by the slowly course of the narrowing process. Rios-Montenegro first reported CRM and a carotid-cavernous fistula in a PXE patient in 1970 [3]. Afterwards three other cases were described [2,4,5], and ischemic stroke and amaurosis fugax occurred in two of these cases [4,5].

Compared to the typical angiographic features of Moyamoya disease (MMD) our case showed a segmental agenesis involving the intracavernous ICA and the development of collateral vessels limited to the carotid siphon dural vessels. The so called “puff of smoke” collateral circulation was not recognizable; there was a well developed dural pial collateral circulation through the frontal branch of the middle meningeal artery. This kind of transdural angiogenesis is remote from the site of occlusion and usually represents the final step in the evolution of MMD, whereas in our case it was detected with an apparently efficient collateral circulation through the circle of Willis and leptomeningeal collaterals.

CRM is observed in angiographic investigations with a frequency of about 1/10,000. It is associated with the hypoplasia or aplasia of the ICA but its exact pathogenesis remains unknown. CRM is regarded as a congenital defect, probably as a consequence of late (fetal or perinatal) regression of ICA which induces the growth of newly developed collateral network not dependent on the embryonic arteries which had already regressed and are no longer available for collateral circulation. A genetic background is also expected based on the high frequency of this condition among Asian, especially Japanese, populations.