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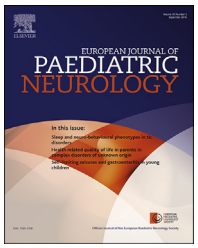

Case Study

Moyamoya syndrome and 6p chromosome rearrangements: Expanding evidences of a new association

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ABSTRACT

Background: Moyamoya syndrome represents an etiologically heterogeneous cerebral evolutive angiopathy. It can be associated with both well-characterized and recently described genetic conditions with mendelian inheritance.
Case report: We report the case of a moyamoya angiopathy in a prematurely born girl affected by congenital heart defect, mild facial dysmorphism, mild neurodevelopmental delay and borderline cognitive profile, associated to a *de novo* complex rearrangement involving the terminal segment of the short arm of chromosome 6.
Conclusion: To the best of our knowledge, this is the second case described of pediatric moyamoya syndrome associated with a 6p complex rearrangement. Adding this case to the pertinent literature, we discuss the pathogenic role of rearrangements in 6p region in moyamoya syndrome and suggest to investigate in this region potential genes involved in angiogenesis or vascular homeostasis.

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1. Introduction

Moyamoya is a severe angiopathy of the internal carotid arteries with associated development of a network of collateral vessels radiographically appearing as a "puff of smoke" (moyamoya in Japanese). When this phenomenon is associated with other neurological or extra-neurological conditions it is referred to as "moyamoya syndrome" (MMS).

Moyamoya may be due to acquired factors (e.g. cranial irradiation) or related to clinically well-characterized genetic diseases (e.g. Alagille Syndrome, Noonan Syndrome, Sickle cell disease, Neurofibromatosis type1, Down syndrome, Turner syndrome, Costello Syndrome). Recently, other genetic conditions have been associated with moyamoya angiopathy, such as those due to defects of *BRCC3/MTCP* and *GUCY1A3* genes.[1]

In children, MMS is frequently characterized by a more aggressive course than in adults. In view of the longer disease history, children have a higher likelihood of disease progression and therefore a higher risk of ischemic/hemorrhagic lesions and, ultimately, of poor neurological outcome. An early diagnosis of moyamoya allows early medical and surgical interventions in the attempt to slow disease progression and to at least partially prevent long-term consequences.[6]

Based on increasing evidence of association of MMS with known or new genetic conditions, it is important to maintain a high index of suspicious for MMS in children carrying a genetic condition, particularly if they experience stroke or recurrent transient ischemic attacks.

We present the case of a girl diagnosed with MMS associated to a complex chromosome rearrangement involving region 6p.

2. Case study

We report the case of a Caucasian girl, only child to non-consanguineous parents, who previously had three miscarriages for unexplained reasons. The girl was born by urgent cesarean section performed at 32 + 6 weeks of gestation because of preterm premature rupture of membranes.

Apgar index was 6–7–8 respectively at 1'–5'–10' minute. Neonatal weight was 1690 gr. After birth she had respiratory distress syndrome requiring invasive ventilation for about 48 h, apneas, jaundice of prematurity and detection of heart defect (inter atrial defect and patent ductus arteriosus). Clinical examination revealed some dysmorphic features, including flat nasal bridge, broad philtrum, upslanted palpebral fissures, micrognathism, anteverted nares, and short neck.

QFQ-banding karyotype (at 500-band level) demonstrated in all metaphases a partial duplication of one 6p and subtelomeric deletion on the same 6p chromosome: 46,XX,der(6) dup(6)(p24p23)del(6)(p25). CGH-array (median resolution of 600 kb, NCBI36/hg18) confirmed the complex chromosome abnormality characterized by a *de novo* terminal deletion of short arm of chromosome 6p25.3 (maximum size 0.6 Mb; 8945–1,489,999 bp) and a *de novo* duplication of short arm of chromosome 6p24.3–6p25.3 (maximum size 9.3 Mb; 1,510,000–10,789,999 bp). An additional interstitial deletion of chromosome 16p13.2 (maximum size 0.6 Mb; 6,310,001–6,889,999 bp), of maternal inheritance, was detected.

Brain MRI, performed at 1 year of age, was normal. The girl was followed-up with rehabilitation and physiotherapy, and she showed a grossly normal motor development (standing at 12 months, walking at 15 months) and a mild language delay (first few-words sentences at age 3 years). The cardiac defect was surgically corrected at 3 years of age. A cognitive scale at age 4 years (Wechsler Preschool and Primary Scale of Intelligence – III) resulted in verbal IQ of 84, performance IQ of 62, and full-scale IQ of 70.

At the age of 4 years and 6 month, the girl was admitted to the emergency department of a peripheral hospital due to sudden onset of vomiting, followed by left hemiparesis and left arm clonic jerking. In the previous four months, the patient had had recurrent episodes of arm (alternating right or left side) or lower limbs weakness, lasting up to 2 h, initially suspected to be epileptic seizures.

At admission the girl was confused and aphasic, with left arm clonic jerks and left hemiparesis. Cardio-thoracic and abdominal examination and vital signs were normal. Seizures were stopped by i.v. phenytoin, following inefficacy of benzodiazepines. Post-ictal EEG showed diffuse slow waves, prevalent on the right hemisphere. Electrolytes, renal and hepatic function tests were normal, and inflammatory markers were negative. Phenytoin was switched to levetiracetam (40 mg/kg per day).

On day 3 after onset, a brain computed tomography showed wide cortical and subcortical hypodensity consistent with a wide ischemic area involving the entire right hemisphere.

On day 4, the girl was transferred to our Pediatric Neurology Unit. The girl was alert, responsive, oriented and had a left central facial palsy and a left flaccid hemiparesis.

Brain magnetic resonance imaging (MRI) showed acute ischemic areas in the territories supplied by the right middle and anterior cerebral arteries (Fig. 1a); brain MRA showed bilateral multiple stenoses of the anterior and posterior cerebral arteries, a high grade stenosis of the right middle cerebral artery (likely involved in the pathogenesis of the stroke) and collateral circulation consistent with MMS (Fig. 1b). Echocardiogram and coagulation studies were normal, and autoimmunity studies were negative. The girl was started on acetylsalicylic acid 5 mg/kg, associated with intravenous fluids. Levetiracetam was maintained.

Two weeks into the admission to our Unit, a digital angiography confirmed bilateral anterior and posterior MMS (Fig. 1c). One month after the stroke, the girl underwent indirect cerebral revascularization by encephalo-duro-arterio-synangiosis of the left hemisphere in order to prevent possible ischemic events in the unaffected hemisphere. The girl also received physical rehabilitation, with good improvement in the lower limb and more limited recovery of the arm, with persistence of poor performance of the left hand. The post-operative period was uneventful.