

Early onset PFAPA-like syndrome in a child with microduplication of the 7q11.23

Sirs,

The 7q11.23 microduplication syndrome (Dup7), leading the duplication of the Williams-Beuren syndrome (WBS) critical region, is a rare contiguous genes disorder characterised by developmental delay with speech and behavioural problems, typical facial dysmorphisms, and congenital abnormalities (1). Brain malformations and seizure are usually associated. Typical craniofacial features are macrocephaly, broad forehead, straight eyebrows, deep-set eyes, high broad nose, short philtrum, thin upper lip and micrognathia. Growth hormone deficiency has been reported in almost 10% of patients. Cardiovascular or genitourinary malformations may be present, and a longitudinal surveillance is required in case of congenital aortopathy (2).

The Periodic Fever with Aphthous stomatitis, Pharyngitis, and Adenitis (PFAPA) syndrome is the commonest autoinflammatory disorder among children, whose classification criteria have been recently reviewed (3). Fevers are usually treated with on-demand steroids. Colchicine or tonsillectomy may be required to arrest the recurrence of episodes (4). The aetiology of PFAPA syndrome is unknown, and polygenic dysregulation of the interleukin 1 beta production has been proposed as the probable cause (5, 6).

Here, we present the first case of early onset PFAPA-like syndrome in a child with partial duplication of the WBS critical region.

A 9-year-old female with diagnosis of PFAPA syndrome presented to our Centre to perform a tonsillectomy. Since 18 months of age, she displayed recurrent fever episodes, every 20 days, characterised by exudative pharyngitis, stomatitis, and cervical adenitis. Pharyngeal swabs were always negative and the episodes spontaneously resolved after 3–4 days. On-demand steroids were required since two years of age due to the onset of febrile convulsions. Electroencephalography was normal and brain magnetic resonance images revealed atypical subcortical white matter abnormalities and hippocampal immaturity. Convergent strabismus of the left eye, usually named Duane syndrome, and language delay were also present. A growth delay was noted, and growth hormone replacement therapy was started without benefit.

At our evaluation, weight and height were under the third percentile for sex and age.

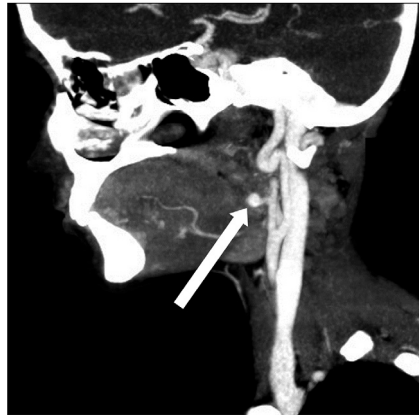


Fig. 1. Computer tomography image shows carotid kinking and aneurism of the retro-tonsil tract of the facial artery (arrow).

She presented macrocephaly, facial dysmorphisms, and mental delay of five years on the Griffiths mental development scale. The array-comparative genomic hybridisation analysis revealed a *de-novo* 1.6 Mb duplication of the chromosome 7, consistent with the diagnosis of Dup7 syndrome. Furthermore, a next-generation sequencing panel with forty-one genes related to systemic auto-inflammatory disorders was negative. Due to the high frequency of inflammatory attacks and the seizure risk, tonsillectomy was performed. Two weeks later the surgery, she presented a massive oral bleeding and was hospitalised. Computer tomography of the neck revealed a bilateral carotid kinking and aneurism of the retro-tonsil tract of the facial artery (Fig. 1), which required urgent embolisation. After two years, the patient has not reported any further episodes of fever.

The complex phenotype of Dup7 syndrome is related to a dosage-sensitive effect of the duplicated WBS critical region caused by genes methylation changes (7). The presence of *NCF1* gene in the duplicated region of our patient suggests an association with the early-onset recurrent fevers. The *NCF1* gene codified for the neutrophil cytosolic factor-1, also known as p47-phagocyte oxidase, a key component of the NADPH oxidase complex that is known to be up regulated in PFAPA patients (8). Furthermore, tonsillectomy was effective in our patient as usually reported in PFAPA syndrome. The higher risk of haemorrhage complications in patients with chromosome disorders characterised by vascular abnormalities should be carefully evaluated before prescribing tonsillectomy.

In conclusion, we report for the first time a case of PFAPA-like symptoms in a child

with the Dup7 syndrome. Further functional analyses are required to confirm that the *NCF1* gene duplication may explain this association.

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