Muscle hemihypertrophy syndrome with PIK3CA gene mutation associated with Tourette syndrome

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INTRODUCTION

The PIK3CA mutation-related overgrowth syndrome or spectrum (PROS) is a group of heterogeneous diseases characterized by a segmental hypertrophy linked to a post-zygotic gain of function mutation in the PIK3CA gene. The PIK3CA gene encodes PI3-kinase, an enzyme involved in the PI3K-AKT-mTOR pathway, one of the major pathways of cell growth.

Here we report the case of a girl with a muscular hemihypertrophy associated with a PIK3CA gene mutation and Tourette syndrome (TS), which we consider a non-random association.

CASE REPORT

This 9-year-old girl was referred for hypertrophy of the left upper limb and left hemithorax since birth (Fig 1). She was born as the first child from healthy and non-consanguineous parents. Pregnancy was marked by intrauterine growth retardation. Birth weight was 2520 g and birth length was 46 cm. Hemihypertrophy of the left arm and hand was noted immediately after birth. The hypertrophy was more pronounced on the thenar eminence, with an enlarged palm and abnormal palmar folds (Fig 2). There was no functional impact. There were no other pertinent exam findings. Whole-body magnetic resonance imaging showed isolated muscle hypertrophy over the left upper limb. The injected magnetic resonance imaging of the brain did not reveal abnormality.

The molecular genetic analysis on a skin biopsy of the affected member showed a post-zygotic heterozygous missense variation c.1633G>A, which predicts p.Glu545Lys in PIK3CA. Quantitative PCR for the PIK3CA mutation c.1633G>A determined a fraction of 15% of mutant DNA in the affected skin tissue.

No progression of the muscular hypertrophy was noted. At 10 years of age, the patient developed daily verbal tics (screams, sounds, isolated words, and echolalia) and motor tics (upper limb spasms), associated with significant anxiety and difficulty in falling asleep. The diagnosis of TS was assessed and aripiprazole was prescribed with clinical monitoring.

DISCUSSION

Isolated congenital muscular upper limb overgrowth with aberrant hand muscles is known to be a condition which can be included into PROS. To our knowledge, only 6 similar cases with an evidenced
PIK3CA mutation have been reported in the literature since 2014 and the identification of the PROS.

The clinical presentation appears stereotyped in the light of these different cases, with the involvement of one or both upper limbs, the presence of muscular hypertrophy or ectopic muscles, the absence of other associated malformations, and the stability of this malformation, which does not progress over time.

TS is a complex disorder characterized by repetitive, sudden, and involuntary movements or vocalizations, called tics. TS is estimated to have a prevalence of 0.3%-0.9% in children. TS has demonstrated to be one of the most heritable, non-Mendelian, and neuropsychiatric disorders. Environmental as well as genetic factors seem to be involved in the pathophysiology. Indeed, in recent years, several new candidate genes involved in multiple neuronal systems, have been identified. In particular, Hildonen et al investigated genome-wide methylation patterns in 16 monozygotic twin pairs, and found a differentially methylated position significantly associated with TS within the promoter region of TSC1 (TSC complex subunit 1). TSC1 regulates signaling of mTOR, which belongs to the PI3K/AKT/mTOR pathway, also known to be associated with neuropsychiatric disorders (depression, schizophrenia, epilepsy, and autism spectrum disorder). This pathway is implicated in the negative regulation of activation and expression inflammatory cytokines that could be involved in the development of neuroinflammations and neuropathology of central nervous system diseases. A dysregulation of this pathway appears to be a risk factor for the development of TS. In addition, a 2017 trial on mice showed that a PI3K inhibitor had beneficial effects on the signs of TS.

TS has not been reported in association with PROS syndrome until now. But intellectual deficits, autism, and more rarely behavioral disorders such as attention-deficit hyperactivity disorder, obsessive-compulsive tendencies, and anxiety-related issues, have been previously reported in patients with hemimegalencephaly with capillary malformation (MCM syndrome) which also belongs to PROS.

Hence, we report the association of congenital muscular upper limb overgrowth with aberrant hand muscles linked to a mutation of the PIK3CA gene and TS. This association supports the emerging evidence for the involvement of the PI3K/AKT/mTOR pathway in the development of TS. This association allows for the development of targeted effective treatments for patients with these disorders.

Conflict of interest
None disclosed.

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Fig 1. Photo of both palms showing hypertrophy of the left thenar eminence.

Fig 2. Photo of the hypertrophy of the left upper limb and left hemithorax.
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