Circumferential Skin Creases and Blepharophimosis are Features Associated With Tubulinopathies: a Case Report and Review of Literature

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Introduction

TUBA1A mutations lead to a large spectrum of severe cerebral malformations such as lissencephaly, microlissencephaly, polymicrogyria, hypoplasia or agenesis of corpus callosum and cerebellar hypoplasia. Epilepsy and severe developmental delay are constantly associated. Dysmorphic features are hardly ever described in patients reported in the literature.

Materials and methods

- Describe new clinical features associated with *TUBA1A* mutation
- Review the differential diagnosis for patients with corpus callosum agenesis and blepharophimosis
- Compare patients with the mutation p.(Arg390Cys) in *TUBA1A* and patients with *TUBB* or *MAPRE2* mutations.

Case report

Family history: Unrelated healthy parents, healthy little sister

Pregnancy and neonatal period:
Normal antenatal US, born at 40 weeks 5/7
Weight: 3kg058 (-1SD), Height: 49cm (0SD),
OFC: 31,8cm (-2,5SD)

At 7 weeks:
West syndrome (Rp/Phenobarbital, Keppra, Sabril)

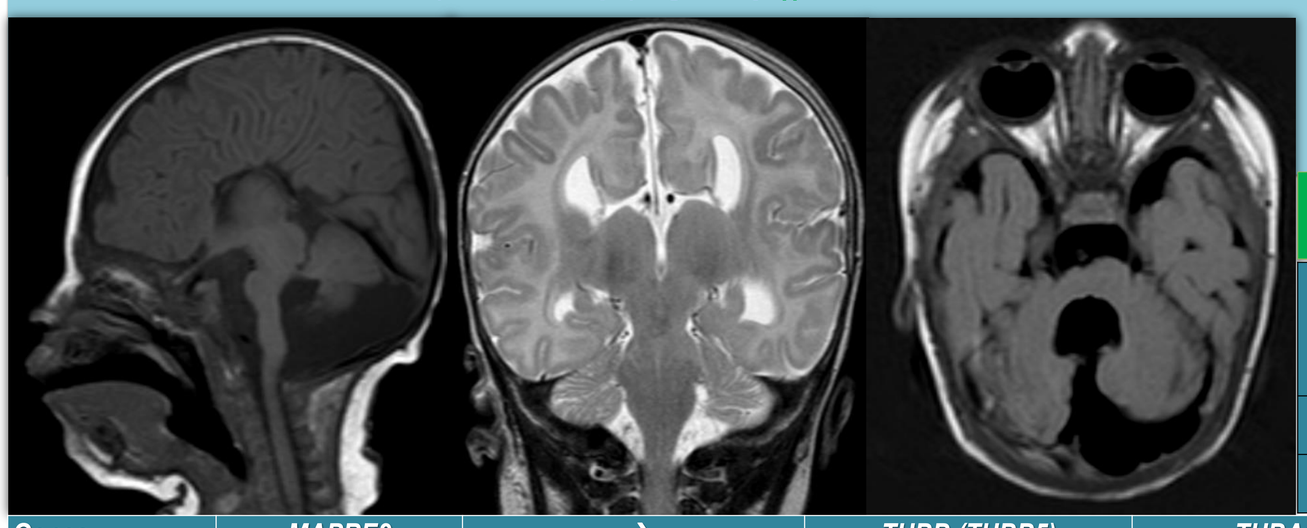
At 18 months:
Surgical correction of bilateral palpebral ptosis, circumferential skin creases in forearms noted

At 5 years:
- Stable epilepsy with rare episodes of absence
- Able to eat small pieces, rare wrong track with liquids
- Ophtalmologic follow up for blepharophimosis, ptosis, myopia, astigmatism and nystagmus
- Orthopaedic corset for scoliosis
- Unable to walk, says a few words, relatively good comprehension

Clinical features (table 1):
Height: 1m (-2.4SD), Weight: 15kg (-1.7SD),
OFC: 47,1cm (-2,8SD)

Genetic investigations

A targeted **gene panel for cerebral malformations** demonstrated a *de novo* likely pathogenic mutation ***(c.1168C>T, p.(Arg390Cys)) in TUBA1A***



Differential diagnosis of blepharophimosis and corpus callosum agenesis

KAT6B	10q22.2	Ohdo syndrome (SBBYSS)
	10q22.2	Genito-patellar syndrome
MAPRE2	18q12.1-q12.2	Circumferential Skin Creases Kunze type
TUBB	6p21.33	

Genes	*MAPRE2*	→	*TUBB (TUBB5)*	*TUBA1A*	→	→	*TUBA1A*
	M2 *p.Asn68Ser* (Isrie et al; 2015)	**M8 *p.Tyr87Cys* (Isrie et al; 2015)**	**M15 *p.Tyr222Phe* (Isrie et al; 2015)**	**Our patient *p.Arg390Cys***	***p.Arg390Cys* (Kumar et al; 2010)**	***p.Arg390Cys* (Poirier et al; 2015)**	**35 patients In littérature**
Inheritance	Homozygous	Homozygous	*De novo*	***De novo***	*De novo*	*De novo*	*De novo* (33), mosaic in mother (2)
Age	15 months	19 years	18 months	**5 years**	Not specified	1 year	4 weeks to 8 years
Microcephaly	No	Yes	Yes	**Yes**	Not specified	Yes	Micro- (13), Normo- (3), Not described (19)
Creases	Limbs and neck	Limbs ; improvement but visible	Limbs	**Forearms; disappeared**	Not described	Not described	Simian creases (1)
Facial features	Flat face, microphthalmia, short palpebral fissures, epicanthal folds, low broad nasal bridge, cleft palate, low-set, small dysplastic ears	Elongated face, hypertelorism, epicanthic folds, upslanting palpebral fissures, microphthalmia, strabismus, wide nasal bridge, aberrant teeth, cleft palate, low-set posteriorly rotated ears with overfolded thick helices	Elongated flat face, hypertelorism, upslanted blepharophimosis, epicanthus, periorbital fullness, long eyelashes, broad and depressed nasal bridge, microstomia, down-turned mouth, malformed low-set ears	**Flat round face, blepharophimosis, ptosis, gingival hypertrophia, small and spread teeth, small and low-set ears with thick helices**	Not described	Convergent strabismus	Sloping forehead (2), microphtalmos (2), hypotelorism (2), hypertelorism (1), upslanding (1), long palpebral fissures with long eyelashes (1), strabismus (4), esotropia (1), epicanthus (1), bulbous nasal tip (1), flat nasal bridge, anteverted nares (1), large mouth (1), high arched palate (1), micro - retrognathia (4), simplified anthelix (1)
Brain MRI	Mildly dilated lateral ventricles, corpus callosum hypoplasia	Hypoplastic vermis, hypoplastic corpus callosum, mild dilatation of ventricles	Hypoplasia of corpus callosum, Dandy-Walker malformation	**Complete corpus callosal agenesis, cerebellar vermis hypoplasia, enlargement of fourth ventricle, retro-cerebellar cyst, discrete hypoplasia of brainstem**	Simplified gyral pattern, complete corpus callosal, agenesis, moderate cerebellar hypoplasia, cortical-white matter interface mildly irregular in places	PMG, dysmorphic basal ganglia, dysplastic cerebellar vermis, severe hypoplasia of brainstem, corpus callosal hypoplasia	Asymmetry/dilatation lat. ventricles (5), enlarged 4th ventricle (2), cortical dysgenesis (1), dysmorphic frontal lobes (1), simplified gyral pattern (3), polymicrogyria (5), lissencephaly (31), corpus callosum hypoplasia/agenesis (23), basal ganglia hypoplasia (5), cerebellar hypoplasia (27), brain stem hypoplasia/dysmorphism (11), hydranencephaly (2), hypoplastic optic nerves (1), absent olfactory bulbs (1), occipital atrophy (1)
Developmental delay	Moderate/severe	Profound	Mild developmental delay	**Severe**	Not described	Not described	Moderate (1), Severe (14)
Neurological features	Epilepsy	Deafness, epilepsy,	/	**Epilepsy (west syndrome)**	Epilepsy	Epilepsy	Epilepsy (35), hypotonia (5)
Others	Hypoplastic scrotum, coronal hypospadias	Short neck, wide-spaced nipples, Ureterocele, hypospadias, cryptorchidia, syndactyly 2,3	Wide-spaced nipples, syndactyly 2,3	**Knees contracture, scoliosis, feet varus**	Not described	Not described	Edema of the hands and feet (1), pectus excavates (1), hypoplasia of labia minor (1), congenital cataract (1), hirschprung (1), SIADH (2), nephrocalcinosis (1), camptodactyly (1), slender fingers and toes, foetal finger pads (1), contractures of the lower limbs (4), spina bifida occulta (1)

Conclusion

- Mutations in *TUBA1A, TUBB* and *MAPRE2* lead to overlapping phenotypes with association of corpus callosum agenesis/hypoplasia, circumferential skin creases and blepharophimosis.
- This might be explained by the complementary function of their encoded proteins (α-tubulin, β-tubulin and microtubule associated protein) which have a role in early brain development (gastrulation, 14-15th weeks).
- α-tubulin interacts with β-tubulin to form microtubules and the structure is stabilized by the microtubule associated protein in cytoskeleton. This structure have a major function in neurogenesis, neuronal migration and differenciation,
- The similar dysmorphic features in our patient compared to patients with Circumferential Skin Creases Kunze type syndrome might be due to a specific effect of our mutation. Alternatively, blepharophimosis and abnormal circumferential skin creases might be frequent but underreported features in patients with *TUBA1A* mutations.

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