Confirmation of an Association Between CTNNB1 Mutations and Hyperekplexia

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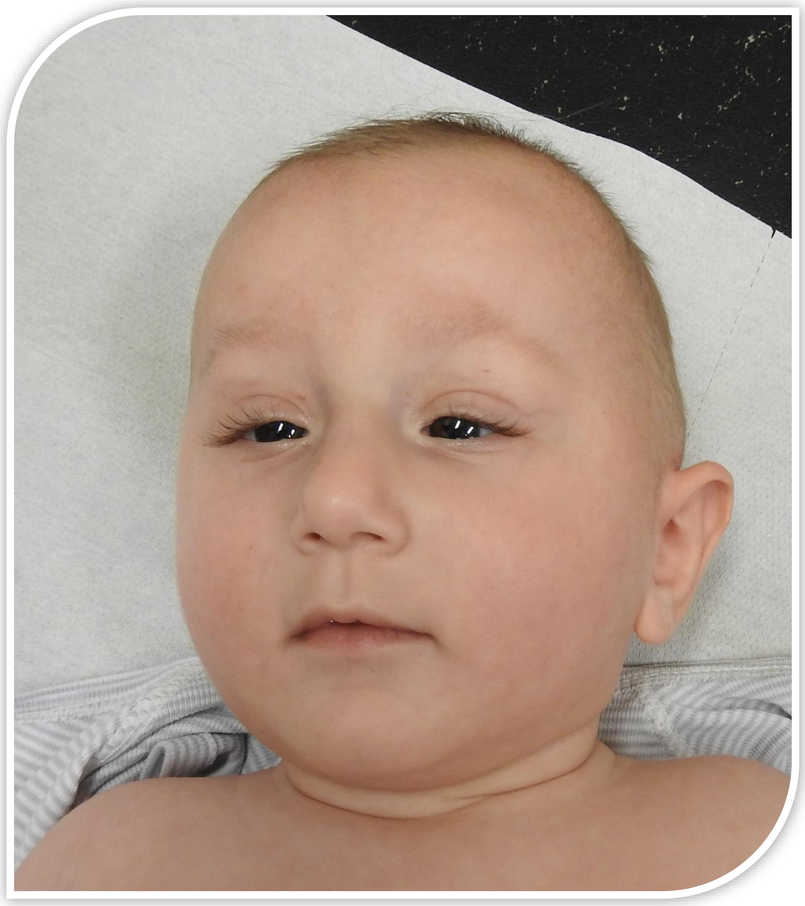
Introduction

Hyperekplexia (OMIM 149400) is a pathology with amplified motor startle reflex to visual, auditory or tactile stimuli. It is defined by three major clinical symptoms: excessive startle reflex, stiffness and generalized stiffness following startle. The consciousness is conserved during the episode. The physiopathology is characterized by an anomaly in the glycinergic pathway. Mutations of the inhibitory glycine receptor, localized in postsynaptic membrane of glycinergic and GABAergic/glycinergic, neurons was identified.

Actually, five genes are involved in hyperekplexia. In 80% of cases, GLRA1 gene encoding a part of glycine receptor's α sub-unit is mutated. In the other cases, SCL6A5 (presynaptic sodium and chloride-dependent glycine transporter 2), GLRB (postsynaptique β sub-unit), GPHN (gephryn), ARHGEF9 (collybistin) mutations are implicated. They can be recessive or dominant and related to the X for ARHGEF9. The prevalence is unknown and North-European patients are more frequently affected.



Clinical report

Family history
- Unrelated parents (Belgian)
- Unilateral renal agenesis in mother
- Healthy older brother

Pregnancy
- Normal

Birth
Weight: 2,725kg (-2 SD). Height: 50cm (-2 SD). OFC: 32,5cm (-3 SD)

3 months
Surgical correction of bilateral congenital ptosis.

4 months OFC: 38,5cm (-2,5 SD)
He presented repeated episodes of generalized hypertonia and hyperextension with eye revulsion. His parents described uncoordinated movements of the four limbs after mild stimuli. Investigations confirmed an hyperekplexia. A treatment by clonazepam was instigated.

6 months OFC: 40cm (-2,5 SD)
Clinical features:

Congenital bilateral ptosis, microcephaly, horizontal palpebral fissures, impression of epicanthus, ptosis (D>G), thin upper lip, small mouth, axial hypotonia and peripheral hypertonia.

Investigation at 4 months for the diagnosis of hyperekplexia
MRI:
- Normal

Prolonged EEG:
- Absence of any paroxysmal activity

Blood and LCR:
- Normal

Metabolic analysis:
- Normal

Genetic analysis

- **Array CGH** analysis was normal (arr(1-22)x2,(XY)x1).
- **GLRA1, GLRB and SLC6A5** genes analysis revealed no anomaly (sequencing and MLPA).
- **Gene panel analysis for neurodevelopmental disorders** identified a de novo ***CTNNB1* mutation c.1796_1799del** in the heterozygous state.

Gene	cDNA change	Protein change	OMIM	Protein function
CTNNB1 3p22.1	NM_001904.3(CTNNB1):c. 1796_1799del	p.Phe599Cysfs*14	116806	Beta-catenin is an adherens junction protein

Discussion

- Our patient presents a haploinsufficiency syndrome of CTNNB1 gene which is very rare. Actually, less than a hundred cases have been reported in the literature.
- In addition to microcephaly and hypotonia, all patients present a developmental delay of varying severity.
- Beta-catenin has a major role in neuronal adhesion and synaptic remodeling.
- CTNNB1 mutation associated with hyperekplexia has been reported once before[1].
- By this case, we confirm the association of CTNNB1 mutation with hyperekplexia and extend the genes which should be investigated in this rare pathology.

References

1. A. Winczewska-wiktor, M. Badura-Stronka, A. Monies-Nowicka, A *de novo CTNNB1* nonsense mutation associated with syndromic atypical hyperekplexia, microcephaly and intellectual disability: a case report, BMC Neurol, 2016; 16:35
2. Fengping Dong, Joanna Jiang, Colleen McSweeney, Donghua Zou, Long Liu, Yingwei Mao, Deletion of CTNNB1 in inhibitory circuitry contributes to autism-associated behavioral defects, Hum Mol Genet. 2016 Jul 1; 25(13): 2738–2751
3. Estelle Dubruc,Audrey Putoux, Audrey Labalme, Christelle Rougeot, Damien Sanlaville, Patrick Edery, A New Intellectual Disability Syndrome Caused by CTNNB1 Haploinsufficiency, Am. Journ. of Medical Genetics, 2014