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Gratis

Case Report

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Lissencephaly: Variant of LIS1 without Cerebellar Hypoplasia

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Abstract

Classic lissencephaly is a rare and serious brain malformation classified in type 1 and type 2. Type 1 is associated with mutations in the human LIS1 gene, which are numerous and constantly discovered. We present a case of isolated fetal ventriculomegaly with subsequent and unexpected diagnosis of neonatal lissencephaly. The clinical manifestation does not match the genotype, often associated with cerebellar hypoplasia.

Keywords: Genetics, Lissencephaly, Magnetic resonance, Prenatal diagnosis, Ultrasound

Introduction

Classic lissencephaly is a rare brain malformation caused by defective neuronal migration during embryonic development. Lissencephaly is classified in type I or 'classical' and type II or 'cobblestone'. The classical form is linked to a primitive neuronal migration failure, in contrast, the second type is attributed to a defect of the pial-glial layer of the brain, which causes an abnormal neuroglial overmigration into the arachnoid space resulting in the formation of an extracortical layer responsible for the agyria and/or a "cobblestone" surface of the brain with ventricular enlargement [1].

Affected children typically have psychomotor disability and drug-resistant epilepsy that usually start in the first months of life with infantile spasms progressing sometimes to Lennox-Gastaut syndrome [2]. The radiological feature of type 1 Lissencephaly is characterized by smooth and thickened cerebral cortex with pachygyria/agyria [3]. In the literature, it is reported that type I is associated with heterozygous deletions or intragenic mutations in the LIS1 gene. Variable microdeletions of chromosome 17(p.13.3) including the LIS1 gene and additional critical genes cause Miller-Dieker Syndrome [4].

Different studies show that there is not a relationship between type or position of intragenic mutations in the LIS1 gene and the phenotypic severity [5].

Case Presentation

A 34-year-old woman at 32 weeks of gestation presents

with a unilateral borderline ventriculomegaly (right 11.9 mm, left 9 mm) and slight enlargement of the III ventricle.

Ultrasonography screening in the second trimester reports standard biometrics and fetal anatomy. Family history is negative for congenital abnormalities and consanguinity.

The patient has a body mass index of 24, normal blood pressure, negative serology for TORCH and glycemic curve. Obstetric history is characterized by 2 early spontaneous abortions and a vaginal delivery at term of pregnancy with good neonatal outcome (Female, 2800 gr). The patient performs ultrasound, genetic counselling and neurosurgical consultation at 34 weeks; informed consent is obtained following a full explanation of the procedures undertaken: it was pointed out that ultrasound has an important role in the diagnosis of fetal malformations, according to the guide line SIEOG 2010, but not in the diagnosis of genetic or chromosomal disorders.

The infant neurosurgeon indicates ultrasound monitoring in order to exclude increased ventriculomegaly and fetal magnetic resonance (MR), but the patient decides not to perform it. Ultrasound tests are performed using the Voluson E8 with TA/TV 2D/3D probes (Figure 1). The 35- week neuro-sonographic evaluation displays mild ectasia of the III ventricle associated with left-most ventriculomegaly (12 mm) with no dilatation of the contralateral ventricle and no abnormality of the posterior cranial fossa. The 38-week ultrasound detects a fetal brain ventriculomegaly on the right side (13-16 mm), on the left one (10-11 mm). Precipitate delivery occurs at 38 + 4 weeks of gestational age.

A female baby is born: weight of 3040 gr., Apgar 9/10.

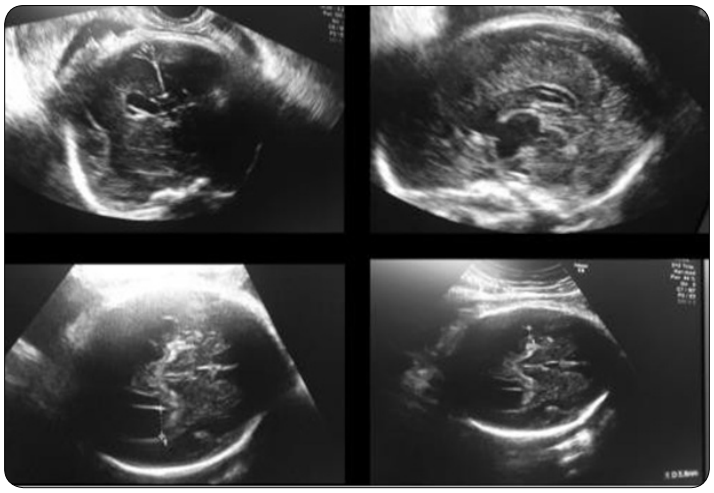

Figure 1: Fetal ultrasound at 32 and 35 gestational weeks: monolateral ventriculomegaly.

At the 11th day brain ultrasound suggests a probable lissencephaly (Figure 2).

The diagnosis is confirmed by cerebral MR with contrast in anesthesia: lateral ventricles appear larger than usual at the level of temporal horns, with no sign of liquoral hypertension; no shift in the structures of the median line, no alterations of the posterior cranial fossa (Figure 2).

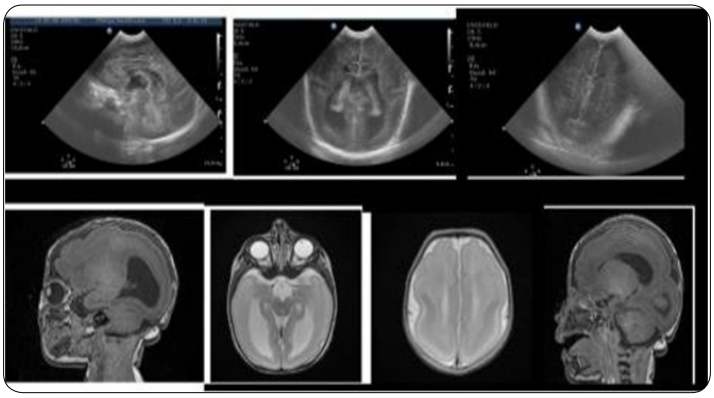

Figure 2: Cerebral ultrasound and Magnetic Resonance at birth: diagnosis of lissencephaly.

After 2 months no critical episodes of epilepsy were observed; psychomotor development and sleep rhythm are normal. FISH is performed for Miller-Dieker.

At 6 months of age, during a fever peak 38.6 °C, the patient shows repeated movements of the upper limbs at the awakening. Since then, the same episodes reappear once or twice a day mainly on awakening. The patient starts a therapy with vigabatrin 250 mg x 2/day.

The electroencephalograms at 2 and 6 months show a poor epileptogenic activity.

At 8 months of age no more critical episodes are observed since the vigabatrin dose is increased to 250 mg in the morning +375 mg in the evening. The patient performs rehabilitation sessions 3 times a week with improvement in head control.

At 10 months neurological examination points out a diffuse hypotonia and lack of trunk control.

At 1 year and 7 months there is a slight progression in the motor control; the patient is able to stabilize the head and manages to sit independently. She starts a therapy with valproic acid up to 50 mg + 100 mg and decreases vigabatrin to 250x2 in 2 months. Parents report “startles”

episodes during sleep with awakening, weeping, frightened looks, occurring isolated or when the patient is overexcited and an episode of generalized tremor during thermal upswing.

At 2 years and 22 days during a hospitalization the patient undergoes genetic research, suspends vigabatrin therapy by introducing valproic acid (100 mg x2 /die), and performs MR, EEG, neurological and vision evaluation.

MR in anesthesia confirms lissencephaly, increased dilatation of the supratentorial ventricular system and III ventricle compared to the previous MR (ventricle of 13 mm vs. 7 mm), the posterior cranial fossa appears normal.

At 2 years and 5 months parents do not observe critical episodes, only "startle" episodes when she is overexcited or irritated. The patient increases valproic acid to 100 mg + 150 mg.

This is the result of genetic research by coding exons of LIS1 gene and direct sequencing: pathogenic variant c.1050 G in heterozygosis causes frameshift and early protein termination [p. (Lys 351Serfs* 4)].

Discussion and Conclusion

The most common Lissencephaly is the isolated type 1 associated with 60% of all heterozygous lesions of the entire LIS1 gene on chromosome 17p.13.3, while the intragenic mutations are less frequent, more than 100 [6,7].

Usually, patients with lissencephaly have psychomotor disability, epilepsy with first life in 82% of cases and low life expectancy. Epilepsy, at first, manifests itself with childish spasms and then becomes more generalized, often tonic-clonic. 88-100% of patients respond to lamotrigine and valproate; patients with lissencephaly associated with mutation of LIS1 also benefit with vigabatrin and phenobarbital [8]. In our case, however, the clinical manifestations are not similar.

The variant of the studied case is reported in literature associated with lissencephaly and cerebellar hypoplasia, particularly of the worm. Some studies on LIS1 mutations correlate clinical severity with the position and type of mutation; in other studies, as in our case, patients with the same mutations have different degrees of neurologic abnormalities [9,10].

The evaluation of the phenotypic effects of the various mutations of LIS1 helps to understand the function of the protein and the search for any additional regulatory factors of neuronal migration [5,7].

Declarations

The manuscript contains original unpublished work and is not being submitted for publication elsewhere at the same time.

The authors declare no conflict of interest; all contributors have read and approved the submission to the Journal.

Informed consent for publication is obtained following a full explanation of the procedures undertaken. There are no sensitive data related to the specific identity in the text or in the figures.

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