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Case Report

A familial case of diffuse periventricular nodular heterotopia identified prenatally: Filamin A defect as the probable cause ☆

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ABSTRACT

Periventricular nodular heterotopia (PNH) is a neuronal migration defect characterized by the presence of ectopic grey matter nodules adjacent to the walls of the lateral ventricles. The main genetic etiology of PNH are variants in the Filamin A gene (*FLNA*, MIM #300049), located in the X chromosome. It affects mostly females (embryonic lethality in males), with about 50% of cases inherited from healthy mothers or with a mild phenotype. It is associated with epilepsy (75%-90%), cardiovascular (65%) and pulmonary pathologies (25%).

A 28-year-old primigravida was referred for prenatal care in obstetrics department because of personal history of obliterative bronchiolitis. She has a family history of asthma (mother and sister) and adulthood-onset epilepsy (father). The pregnancy was uneventful up to 20 weeks and 3 days when bilateral periventricular irregularities and mega cisterna magna were identified on ultrasound in a female fetus. Neurosonography was performed, which led to the hypothesis of diffuse PNH, supported by MRI. The hypothesis of PNH associated to the *FLNA* gene was made. Brain MRI on the pregnant woman was requested, which confirmed a similar pattern of PNH. The arrayCGH (PerkinElmer, Prenatal filter 37K) was nor-

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mal, and whole exome sequencing identified the likely pathogenic c.1554del p.(Val519fs*) variant in the *FLNA* gene.

We present a case of X-linked hereditary PNH that highlights the value of fetal neurosonography in making a putative diagnosis. The diagnosis was supported by MRI in both fetus and mother. The investigation was supplemented by genetic studies, which confirmed the diagnosis.

Introduction

Heterotopia is a malformation of cortical development caused by impaired neuronal migration which comprises a group of clinical entities defined by the existence of neurons in locations other than the cerebral cortex. It can be divided into 3 broad clinical categories: periventricular, subcortical and band heterotopia [1].

The periventricular nodular heterotopia (PNH) is the most commonly type of heterotopia in clinical practice [1]. It's characterized by the presence of ectopic grey matter nodules adjacent to the walls of the lateral ventricles that can lead to erroneous connections and epilepsy in varying degrees [2–4]. PNH is a rare condition. Case series estimate that 2% of the adult patients with epilepsy have PNH, which accounts for 20% of cases of malformations of cortical development [5].

PNH is associated with numerous copy number variations (CNVs) and single gene variants and can be part of syndromic disorders [6]. It is associated with mutations in at least 20 genes; the main genetic etiology is the Filamin A gene (*FLNA*, MIM #300049) localized in Xq28 [5]. *FLNA* PNH typically presents a diffuse pattern with bilateral clusters of confluent nodules extending along the walls of the frontocentral lateral ventricles. *FLNA* is responsible for cell stability and motility, and its deficiency is inherited in an X-linked fashion, affecting mostly females (embryonic lethality in males), with around 50% of cases inherited from healthy or mild phenotype mothers. The phenotypic spectrum also includes epilepsy (75%–90%), cardiovascular (65%) and pulmonary pathologies (25%), among others. Identification of *FLNA*-related disorders is of great clinical importance [7]. Although regarded as underdiagnosed during fetal life [8], advances in imaging techniques have allowed prenatal diagnosis of some PNH cases [9-11]. Prenatal genetic counselling in the prenatal setting is challenging because of the unpredictability of the phenotype.

Case report

A 28-year-old primigravida was referred for prenatal care to the obstetrics department because of a personal history of obliterative bronchiolitis. She has a family history of asthma in her mother and sister; her father had epilepsy in adulthood (Fig. 1). She is not consanguineous with her partner, who is healthy and has an irrelevant family history.

The pregnancy was uneventful up to 20 weeks and 3 days when she was referred to our unit. The first-trimester scan was normal, with nuchal translucency measuring 1.0 mm, and without other ultrasound or biochemical markers of aneuploidy screening. A second-trimester biochemical screening was performed, revealing a low risk for aneuploidies.

An anomaly scan was carried out at 20 weeks and 3 days revealing bilateral periventricular irregularities and mega cisterna magna in a female fetus; the remaining organ scan was apparently normal. Subsequently, neurosonography was performed, which identified mega cisterna magna (Fig. 2), borderline ventriculomegaly (Fig. 3), irregular lateral borders of the cerebral ventricles (Fig. 4), large squared dysmorphic frontal horns (Fig. 5), and hyperechoic nodules protruding into the ventricular lumen (Fig. 6). The diagnosis of PNH was considered as the most probable cause that would explain the ultrasound findings. The detected anomalies were discussed with the patient and an amniocentesis was performed.

A multidisciplinary team meeting occurred, comprising experts in Fetal-Maternal Medicine, Pediatric Neurology, Pediatrics and Medical Genetics. Considering the fetus being female and the mother's medical history of lung disease, X-linked *FLNA* gene variant was considered as a probable cause of PNH. As a result, Magnetic Resonance Imaging (MRI) was suggested for both the fetus and the mother. It confirmed the presence of PNH and mega cisterna magna in the fetus (Fig. 7) and identified the same PNH pattern and a mega cisterna magna in the mother (Fig. 8).

Genetic studies were conducted using fetal DNA and included a normal QF-PCR, karyotype and arrayCGH (PerkinElmer, Prenatal filter 37K), followed by Whole Exome Sequencing (WES) with clinical information supporting the main diagnostic hypothesis of PNH associated with the *FLNA* gene. Molecular diagnosis results were expected to be delivered beyond 24 weeks of gestation, which is the legal period for pregnancy termination in Portugal when a fetal malformation is detected. However, following counseling from a Pediatric Neurologist and Geneticist, and considering that PNH was present in both the fetus and mother, with the latter exhibiting a very mild phenotype, the couple decided to continue the pregnancy.

Later, the WES result confirmed the diagnosis of PNH associated with the *FLNA* gene (MIM #300049), identifying the variant NM_001110556.1: c.1554del p.(Val519fs*) in a heterozygous state. This frameshift variant was not previously reported in the literature and was classified as likely pathogenic.

The remaining pregnancy was uneventful, the baby was born at 40 weeks of gestation by eutocic delivery and had an Apgar score of 9/10. The newborn was small for gestational age with length <1st centile, weight in the second centile and head circumference in the 10th centile. The neonatal period was uneventful, and her first observation in

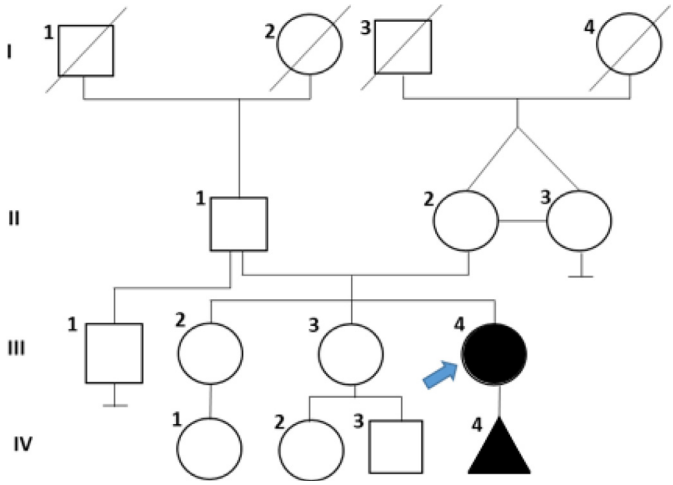

Fig. 1 – Genogram: maternal aunt (III3) and grandmother (II2) have asthma; grandfather (I2) adult onset epilepsy.

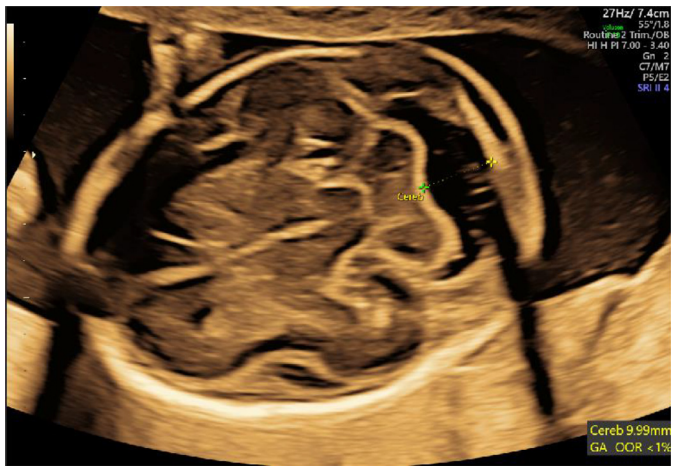

Fig. 2 – Fetal neurosonography: Mega cisterna magna.

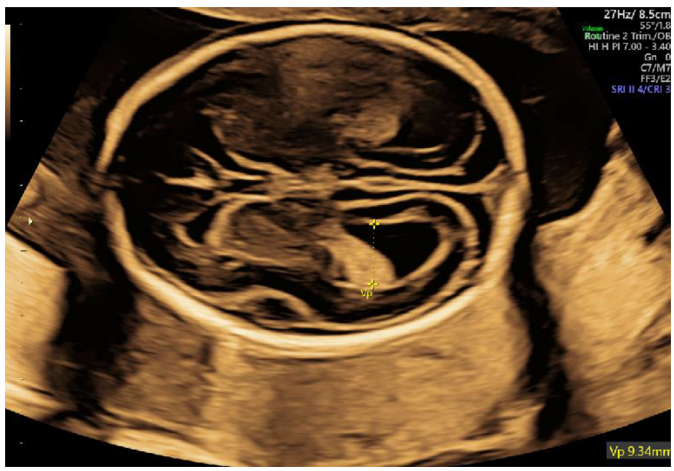

Fig. 3 – Fetal neurosonography: Ventricular atria with borderline width of ~9-10 mm and dysmorphic frontal horns.

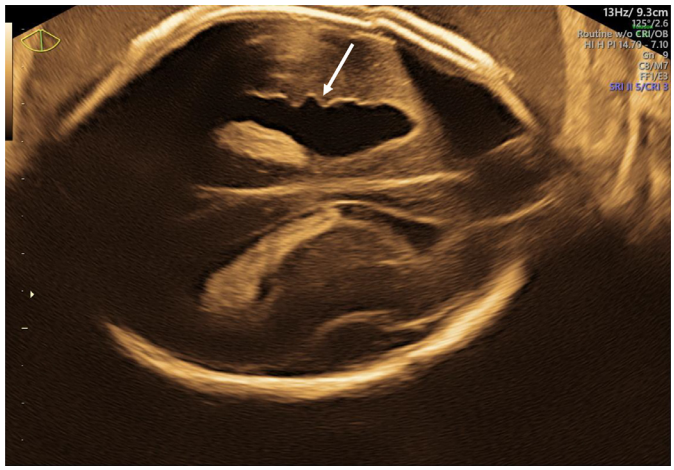

Fig. 4 – Fetal neurosonography: Irregular borders of the lateral ventricles (white arrow).

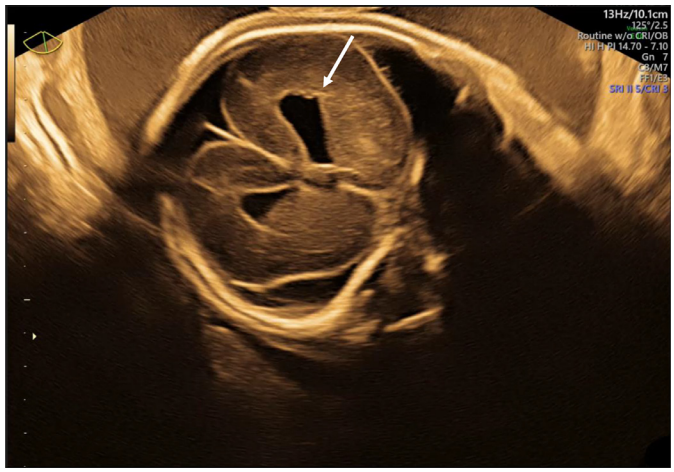

Fig. 5 – Fetal neurosonography: Large squared dysmorphic frontal horns with hyperechoic periventricular nodules protruding into the ventricular lumen (white arrow).

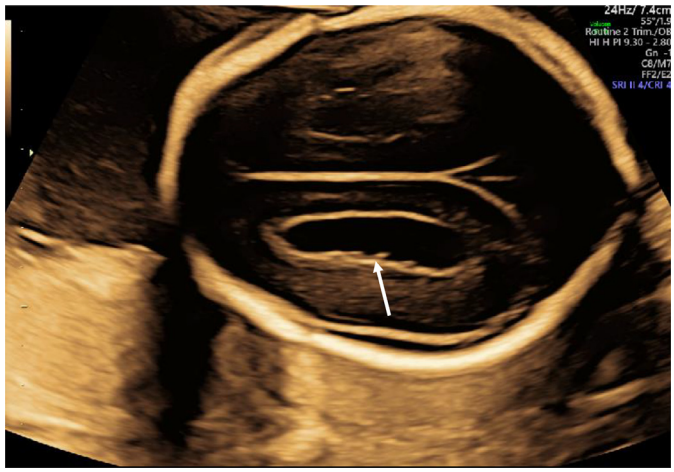

Fig. 6 – Fetal neurosonography: Hyperechoic periventricular nodules protruding into the ventricular lumen (white arrow).

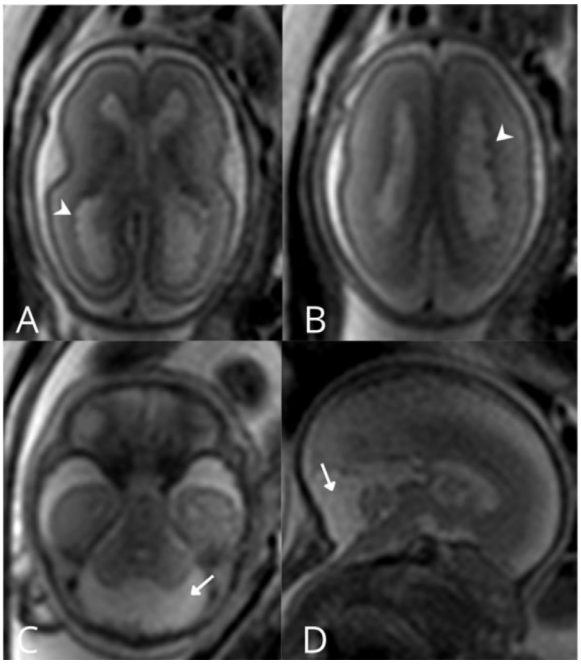

Fig. 7 – Fetal MRI. Diffuse periventricular nodular irregularities shown in axial T2-WI in sequence T2 (A and B, white arrowheads), suggesting periventricular nodular heterotopia; occipital horn enlargement (A). Mega cisterna magna shown in axial (C, white arrow) and sagittal (D, white arrow).

Pediatric Neurology at 1 month was normal. At 6 months old, the infant was reassessed at Medical Genetics and exhibited normal neurodevelopment for her age. The child will continue to have follow-up appointments with a Pediatric Neurologist and was referred to Pediatric Cardiology to surveillance (echocardiogram and baseline evaluation are recommended). It's also necessary to monitor her neurodevelopment and pulmonary symptoms to prompt intervention if necessary.

Additional genetic tests confirmed the presence of the genetic variant in the mother but not in the grandmother. Therefore, cascade studies in other relatives were not recommended. Genetic counseling was performed to explain the potential risk for future offspring, especially in the case of a male fetus. It was concluded that the pulmonary pathology is explained within the context of the *FLNA* variant. Since *FLNA* defects can be associated with cardiovascular pathologies, cardiovascular surveillance was recommended.

Discussion

The literature reports that PNH is usually diagnosed by MRI following ultrasound findings such as mega cisterna magna or ventriculomegaly [8–10]. However, in this case, a detailed neurosonography was the imaging technique that led to the diagnosis of PNH. A *case series* identified several classical ultrasound features associated with PNH, including irregular ventricular borders and nodules protruding into the ventricular lumen [7]. Another reported feature is the presence of large squared dysmorphic frontal horns [7,9], which was also observed in this case.

Regarding imaging techniques, the literature is consistent in indicating a higher sensitivity of MRI (93%) compared with neurosonography (72%) [12]. However, the diffuse nodularity associated with classical bilateral PNH probably improves the sensitivity of the neurosonography in detecting PNH. Conversely, nondiffuse forms with more focal abnormalities are more readily detected by the MRI and may be missed by ultrasound [7].

Regarding prognosis, the largest *case series* of *FLNA* variant adults' carriers shows that the phenotype in females is very variable. Difficult to control epilepsy was the core clinical finding and, in some patients, started in adulthood. The neurodevelopment was normal for almost all PNH patients [13].

Heterotopias in the pediatric population are not so well characterized in the literature. A *case series* highlights the heterogenous nature of the causes in children and the more

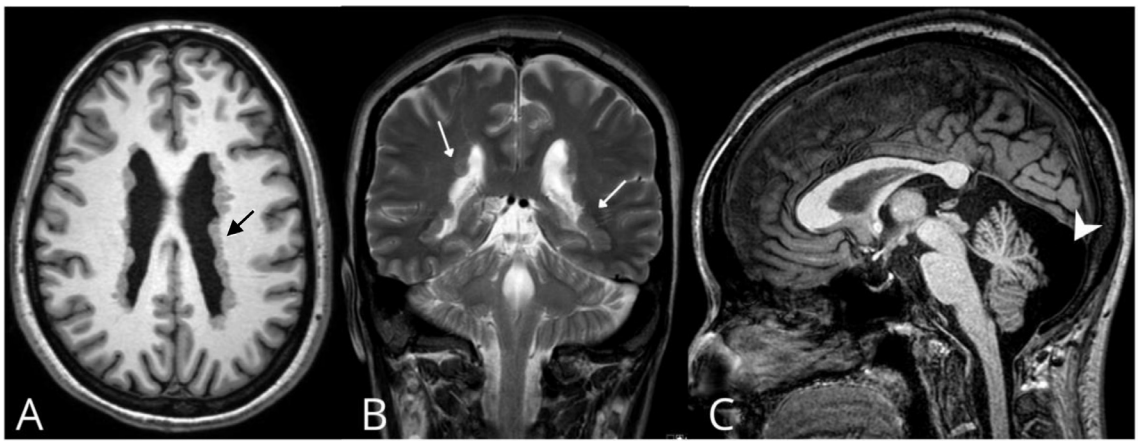

Fig. 8 – Brain MRI of the mother. Periventricular nodular heterotopia shown in axial T1-WI (A, black arrow) and coronal T2-WI (B, white arrow). Mega cisterna magna shown in sagittal T1-WI (C, white arrow head).

frequent association with multiple cerebral and systemic malformations and developmental delay. In contrast with adults, variants in *FLNA* are likely to represent only a minority of the cases diagnosed early [14].

Additionally a *case series* of 30 fetuses with PNH, in which identification of a causative variant in the *FLNA* gene was made in 54% (6/11) of the cases with a diffuse form, describes adequate development in the 5 cases where the pregnancy was continued [10].

Early detection of *FLNA* women carriers is critical. It allows genetic counseling for herself and her relatives including family planning options (prenatal genetic testing or preimplantation genetic diagnosis) and appropriate medical surveillance. The high prevalence of cardiovascular manifestations (especially bicuspid aortic valve and patent ductus arteriosus,) justifies early and repeated cardiovascular surveillance, even in asymptomatic variant carriers [13].

In diffuse PNH, genetic counselling in the antenatal setting is challenging because of the unpredictability of the phenotype. Nevertheless, performing a brain MRI on the pregnant woman may contribute to clarifying the diagnosis, especially in cases of mothers with a mild phenotype.

Conclusion

We present a rare case of X-linked hereditary PNH identified in the prenatal period. This case pinpoints the importance of the fetal neurosonography in the diagnosis of diffuse PNH and suggests that screening for diffuse PNH should be offered to asymptomatic parents of children with the disease. Due to PNH's strong heritability, such screening may support prognosis based on phenotype of the parents.

Author contributions

All authors participated in the medical care offered to the patient; Neves M. and Borges AL. conceptualized the case report; Neves M. and Borges AL. collected data and wrote the manuscript draft; Moldovan O., Loureiro T., Martins G., Sá G., reviewed and edited the manuscript; all authors have approved the final manuscript.

Patient consent

Informed written consent was obtained by the patient.

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