

Fetal hemimegalencephaly associated with SENP7 mutation: about a case

Hemimegalencefalia fetal asociada a mutación en *SENP7*. A propósito de un caso

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Summary

We present a case of a 26-week fetus diagnosed by *in utero* magnetic resonance imaging (MRI) with total left hemimegalencephaly, associated with a *SENP7* gene variant not previously described in this pathology. Hemimegalencephaly is a rare disease, with only a few published cases diagnosed by *in utero* MRI, which consists of an hamartomatous growth of the entire cerebral hemisphere affected, due to a neuronal proliferation and migration disorder which leads to severe neurological alterations. MRI findings of the pathology are described.

Resumen

Se presenta un caso de un feto de 26 semanas al cual se le diagnostica mediante resonancia magnética (RM) fetal hemimegalencefalia total izquierda, asociada con una mutación en el gen *SENP7* no descrita previamente en relación con esta patología. La hemimegalencefalia es una enfermedad rara, con muy pocos casos publicados diagnosticados mediante RM fetal, que consiste en un crecimiento hamartomatoso de todo el hemisferio cerebral afectado, debido a un trastorno de la proliferación y migración neuronal que conlleva alteraciones neurológicas graves. Se describen los hallazgos por RM de dicha patología.

Key words (MeSH)

Hemimegalencephaly
Malformations of cortical development
Nervous system malformations
Magnetic resonance imaging

Palabras clave (DeCS)

Hemimegalencefalia
Malformaciones del desarrollo cortical
Malformaciones del sistema nervioso
Imagen por resonancia magnética

Introduction

Hemimegalencephaly is a rare congenital disease with high mortality. It is classified within the cortical developmental malformations secondary to neurogenesis disorders. It presents with macrocephaly, developmental delay and seizures of difficult pharmacological control.

The main findings identified by magnetic resonance imaging (MRI) are overgrowth of part or all of a cerebral hemisphere, variable degrees of pachygyria, polymicrogyria, neuronal heterotopias and white matter gliosis. The main finding by prenatal ultrasound is unilateral ventriculomegaly. Although it is a rare disease, it is important to suspect it and to know it for a correct prenatal diagnosis.

Case report

A 29-year-old first time pregnant woman, with no relevant personal or family history, showed unilateral left ventriculomegaly on prenatal ultrasound at 23 weeks. Subsequently, at gestational age of 26 weeks and 3 days, a fetal MRI was performed (Optima 450w 1. 5T General Electric) whose findings were compatible with total left hemimegalencephaly, enlargement of the left cerebral hemisphere with malformation of cortical development: dented cortical surface, abnormal cortical sulci and alteration in the opercularization of the left insula, deformity and elongation of the left frontal horn, which showed imprints on its wall secondary to heterotopias and traction of the cavum septum pellucidum towards the left hemisphere. Hypertrophy of the left cerebral peduncle of the midbrain, left hemiprotuberance, left hemibulb and left cerebellar hemisphere was identified. He also showed hypertrophy of the left olfactory nerve, dilatation of the left cortical veins in the extraaxial space and of the posterior third of the superior longitudinal sinus, the straight sinus, the press of Herophilus and the occipital sinus, which decreased the size of the posterior fossa, and thickening of the corpus callosum, although its length was normal. None of these findings were visible on ultrasound. Dilatation of the left ventricular atrium and left occipital horn was also observed, as well as enlargement of the left cranial vault and cerebrospinal fluid (CSF) in the extra-axial space (Figure 1).

The only alterations in fetal biometry were an asymmetry between left (p 75-90) and right (p 25-50) cerebral occipitofrontal diameter; and an elevated anteroposterior diameter of the pons (p 75-90).

The rest of the study was normal. The patient decided to voluntarily terminate the pregnancy and genetic analysis of the fetus identified a de novo variant of uncertain significance in the SENP7 gene.

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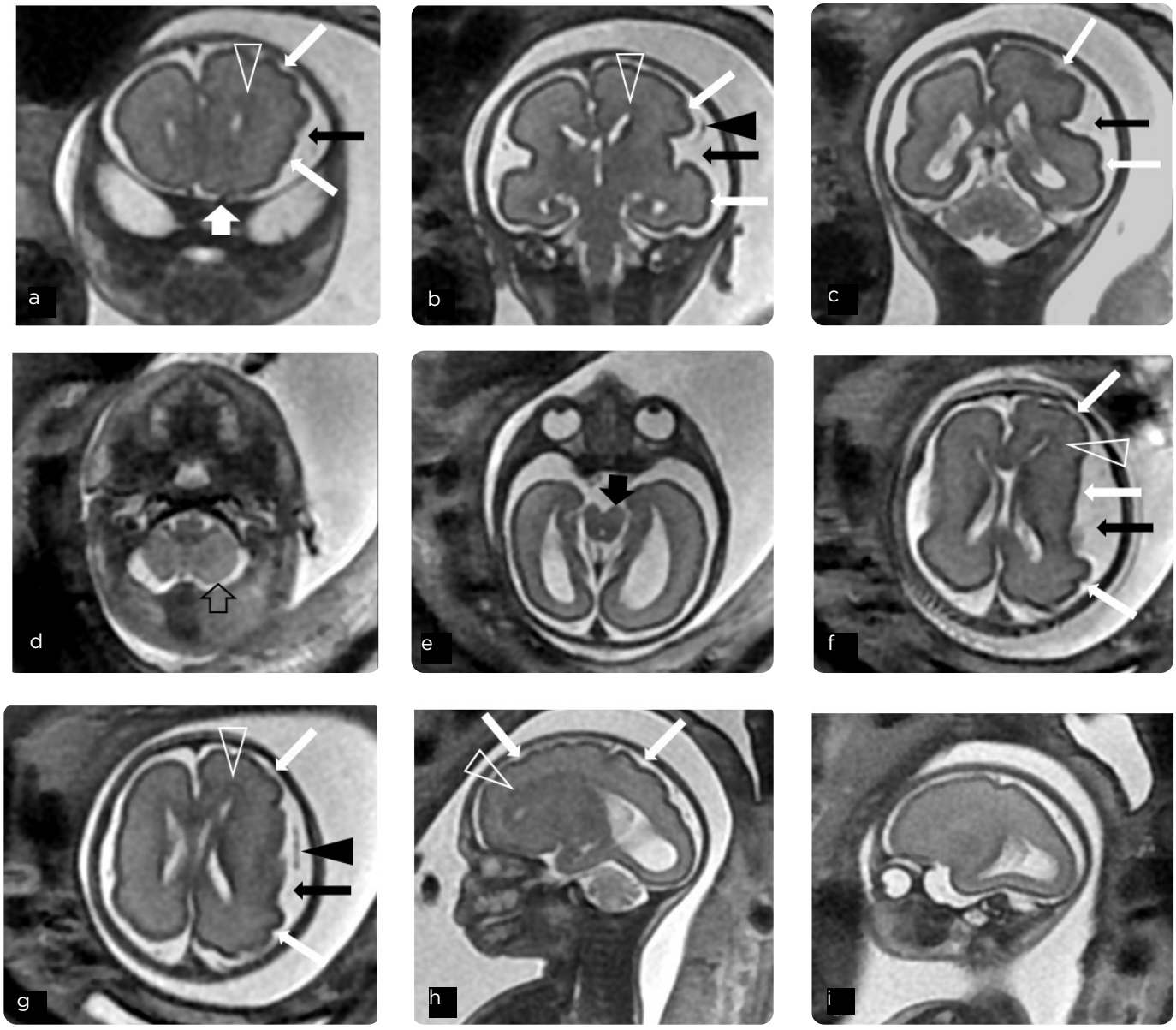


Figure 1. Left hemimegalencephaly. Gestational age 26 weeks and 3 days. a, b and c) Coronal with T2 information. d, e, f and g) Axial with T2 information. h, i) Sagittal with T2 information. Increased size of the left hemisphere with malformation of cortical development with dented cortical surface and abnormal cortical grooves (long solid white arrows). Deformity and elongation of the left frontal horn with heterotopic imprints on its wall (empty white arrowheads). Hypertrophy of the left cerebral peduncle of the midbrain (short solid black arrow in e) and left cerebellar hemisphere (short empty black arrow in d). Hypertrophy of the left olfactory nerve (solid white short arrow in a), as well as dilatation of left cortical veins (solid black arrowheads) and enlargement of the left extraaxial space (solid black long arrows). Right cerebral hemisphere with normal features (i).

Discussion

Neurons and glia of the gray matter of the cerebral hemispheres originate in the ventricular layer (germinal matrix) of the hemisphere between the 5th and 6th week, and must migrate to their final location in the cortex or deep structures (1).

Malformations of cortical development are classified according to the impairment they cause in neurogenesis, proliferation, differentiation, migration or neuronal organization (2).

Hemimegalencephaly is a rare sporadic disease, with an incidence of 1-3 cases per 1000 epileptic children and an equal sex distribution (2).

It is characterized by overgrowth of one cerebral hemisphere. It is also known as unilateral megalencephaly; the term focal megalencephaly is used when only part of the hemisphere is affected (1).

It is due to a de novo somatic mutation in some component of the P13K-AKT-mTOR pathway (PIK3CA, AKT1, AKT3, PIK3R2, PTEN, DEPDC5, TSC2, mTOR) in dorsal brain progenitors, resulting in decreased growth restriction and cell survival, which affects neurogenesis and cell proliferation (3). It subsequently affects the migration and/or differentiation of neurons, causing a disorganization of the tissue architecture with an altered pattern of gyri in that hemisphere (4).

About 50% of cases are associated with neurocutaneous syndromes (epidermal nevus, CLOVES, hypomelanosis of Ito, Klippel-Weber-Trenaunay syndrome, neurofibromatosis 1 or tuberous sclerosis) (4, 5).

Prenatal ultrasound shows unilateral ventriculomegaly, predominantly in the posterior horn of the lateral ventricle. Increased brain circumference, midline deviation (usually occipital) due to hemispheric asymmetry, abnormal sulci and cortical thickening are also observed.

MRI shows overgrowth of one cerebral hemisphere, with deformity of the lateral ventricle and diffuse dilatation and/or rectification or collapse of the frontal horn and/or disproportionate dilatation of the occipital horn (colpocephaly). The midline may be deviated to the contralateral side, especially in the occipital region. The white matter may be enlarged and have decreased signal due to heterotopia, gliosis or abnormal myelination. An abnormal furrow pattern is also identified, manifesting as polymicrogyria, pachygyria and agyria. The dysplastic gray and white substances are heterogeneous, with increased signal on T1-weighted sequences and decreased signal on T2-weighted sequences. There may be thickening of the corpus callosum in the affected area. Diffusion restriction may also be observed due to increased cellularity. In mild cases, the distribution is mainly lobar. In 40% of cases, dilatation of the veins in the affected hemisphere is observed. The ipsilateral cerebellar hemisphere (47%) and brainstem (7%) may be hypertrophied. The cerebellar folia may be bilaterally altered. The ipsilateral olfactory (26%) and optic (3%) nerves may also be hypertrophied (2).

It presents with developmental delay, psychomotor deficits, progressive hemiparesis, intractable epileptic seizures and, if severe, risk of death in the first year of life (6).

The differential diagnosis is made with tumor or intracranial hemorrhage due to increased hemispheric volume and with neuronal migration anomalies such as heterotopias and polymicrogyria (2).

The peculiarity of the case presented lies in the identification of a mutation in the SENP7 gene, which to date has not been described in the literature associated with hemimegalencephaly. The SENP7 protein is a SUMO (small ubiquitin-like modifier) protease involved in the P13K-AKT-mTOR pathway and has been associated, among others, with synapses, neurodegenerative diseases, neurogenesis in early stages of neuronal differentiation (7).

Under normal conditions, in the P13K-AKT-mTOR pathway, PTEN can remove a phosphate from the PIP3 molecule to convert it to PIP2, thus inhibiting signaling through this pathway. PTEN is the most important negative regulator of this pathway and one of the most important tumor suppressors.

The SENP7 protein is also a regulator of this pathway, since it facilitates the SUMOylation/ubiquitination and subsequent degradation of PTEN (8). By degrading the main negative regulator of the pathway, an activation of signaling is achieved as a final result.

The mutation of uncertain significance in this case does not affect the catalytic domain or other known or described domains of the protein, but may result in an improper conformation of the protein. However, it cannot be predicted a priori whether that would lead to protein degradation or simply malfunction. Thus, the mutation could have negative effects on SENP7 function, in that the normal PTEN degradation process is not performed, which could affect neurogenesis and neuronal differentiation, which would explain the etiology of hemimegalencephaly. However, future research is needed to shed light on this issue.

Conclusions

Hemimegalencephaly is a rare pathology that involves severe neurological abnormalities, so it is important to be familiar with its radiological findings and to help in the management and definition of fetal prognosis. It is difficult to diagnose it by prenatal ultrasound, so fetal MRI should be considered if unilateral ventriculomegaly is observed on ultrasound, especially if it is associated with asymmetry or midline deviation.

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