

Hereditary subependymal heterotopia associated with mega cisterna magna: antenatal diagnosis with magnetic resonance imaging

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ABSTRACT

Bilateral nodular subependymal heterotopia has recently been identified as a hereditary disease linked to the X-chromosome. The sonographic findings are very subtle and difficult to observe during the second trimester when the germinal matrix is at its largest. Fetal magnetic resonance imaging facilitates visualization of the periventricular area. We report a case of bilateral nodular heterotopia associated with mega cisterna magna diagnosed by ultrasound and magnetic resonance imaging at 29 weeks' gestation. Magnetic resonance imaging of the brain of the mother revealed similar findings to those observed in the fetus and neonate. This case confirms the association between mega cisterna magna and bilateral periventricular nodular heterotopia and demonstrates that neuroimaging studies of the mother can contribute to the fetal diagnosis.

INTRODUCTION

Hereditary nodular heterotopia is a recently recognized malformation of neural migration in which nodular masses of gray matter line the walls of the lateral ventricles. Most affected individuals are females with epilepsy. The early antenatal diagnosis can be difficult because the germinal matrix can hide the heterotopic nodules. We report a case in which ultrasound and magnetic resonance imaging (MRI) were used to identify bilateral nodular heterotopia associated with mega cisterna magna in a fetus at 29 weeks' gestation.

CASE REPORT

A 26-year-old primigravid woman had an apparently uneventful pregnancy until 26 weeks of gestation, when she

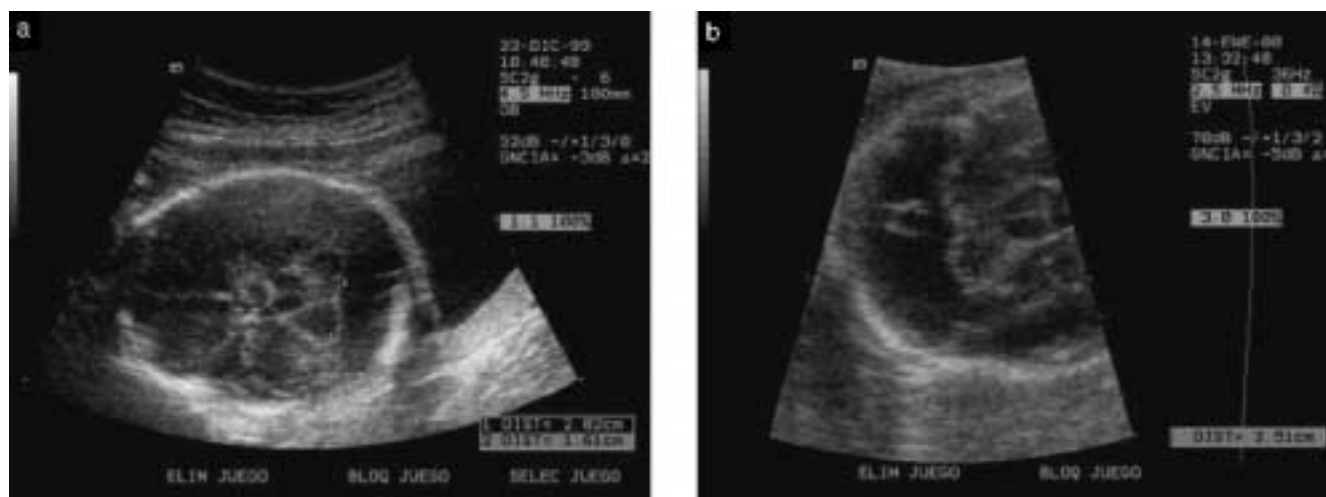


Figure 1 Ultrasound image (axial view) of the posterior fossa. At 26 weeks of gestation (a) the cisterna magna measured 16 mm; 22 days later (b) it had increased to 25 mm.

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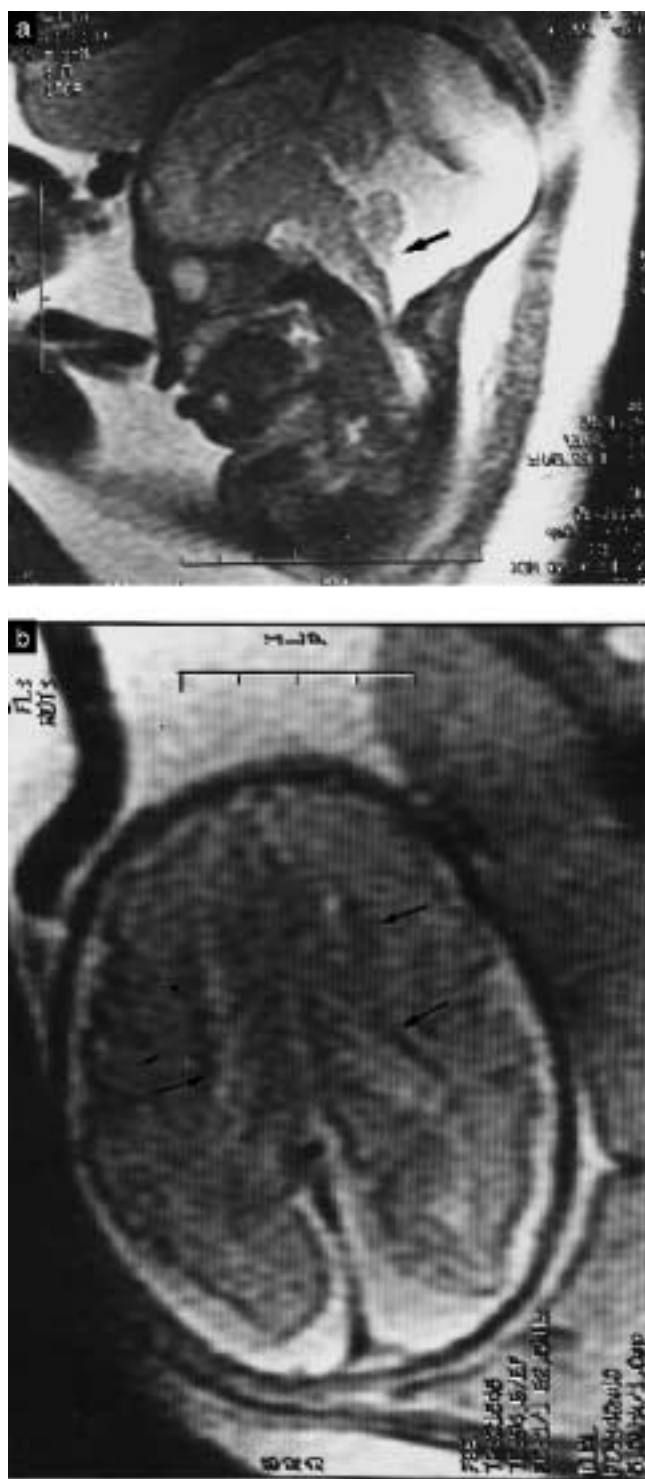


Figure 2 Sagittal magnetic resonance image (a) demonstrating an enlarged cisterna magna with the fourth ventricle well delineated. Axial magnetic resonance image (b) at the level of the lateral ventricle, showing hypointense nodules in the ventricular wall corresponding to heterotopic gray matter.

was referred to our hospital because of a fetal intracranial anomaly detected during ultrasound examination.

At the time of her first visit to our unit, an ultrasound scan was performed which confirmed normal fetal growth and the presence of an apparently isolated, enlarged (16 mm) cisterna

magna. The cerebellum and ventricles appeared normal and there were no other structural anomalies.

Maternal serum TORCH screening was negative. Twenty-two days later another scan showed enlargement of the mega cisterna magna to 25 mm, with the rest of the brain structures being apparently normal (Figure 1). At this time, fetal MRI was performed to clarify the posterior fossa malformation. Imaging was performed on a 1.5-T (1.5-T Sigma, General Electric, Milwaukee, MI, USA) system using a phase array coil and a 4-mm single shot fast spin echo. T2-weighted images were obtained in planes that were approximately sagittal, coronal and axial with respect to the head of the fetus.

The T2-weighted MRI on the sagittal and axial planes confirmed the presence of the cerebellar vermis and fourth ventricle and identified the mega cisterna magna. In addition we observed multiple small nodular subependymal foci of low signal intensity, similar to that of the gray matter, located in the margins of the lateral ventricles. This finding, in addition to the presence of the mega cisterna magna, suggested a diagnosis of nodular subependymal heterotopia (Figure 2).

After counseling, we performed fetal blood sampling for karyotyping, which was normal (46,XY), and a search for biochemical signs of fetal infection, which was negative. Further ultrasound examinations were carried out at 31 and 35 weeks and they showed continuing enlargement of the mega cisterna magna.

At 37 weeks of gestation, onset of labor occurred, and a Cesarean section was performed because of breech presentation and a hyperextended fetal head. A 2770-g male was delivered, with Apgar scores of 4 and 9 at 1 and 5 min, respectively, and an umbilical artery/vein pH of 7.30/7.35; he needed ventilatory support and was admitted to the neonatal intensive care unit. Examination of the neonate revealed persistent ductus arteriosus and cryptorchidism.

Postnatal findings on MRI of the brain were consistent with nodular subependymal heterotopia and mega cisterna magna, with no other brain anomalies (Figure 3).

At 6 months of age, the baby had severe neurodevelopmental delay. Magnetic resonance imaging of the mother's brain was performed and nodular subependymal heterotopia was detected in association with mega cisterna magna (Figure 4).

DISCUSSION

Subependymal heterotopia, also known as periventricular nodular heterotopia (PNH), is a migration anomaly that leads to clusters of disorganized neurons and glial cells persisting as nodules along the lateral ventricular walls^{1,2}. Two different morphological appearances of PNH have been described, namely bilateral and unilateral PNH^{3,4}. The unilateral form usually affects the paratrigonal region and is thought to be determined by a vascular mechanism³. Bilateral PNH has recently been recognized as a new entity that follows an X-linked dominant inheritance pattern⁵⁻⁷. Most affected individuals are females with epilepsy and normal intelligence. Other abnormalities observed in these female groups include persistent ductus arteriosus, bicuspid aortic valve and coagulopathy⁸. There are only a few reports of affected males⁹⁻¹¹, since X-linked inheritance means that development of most of the male embryos fails to progress.

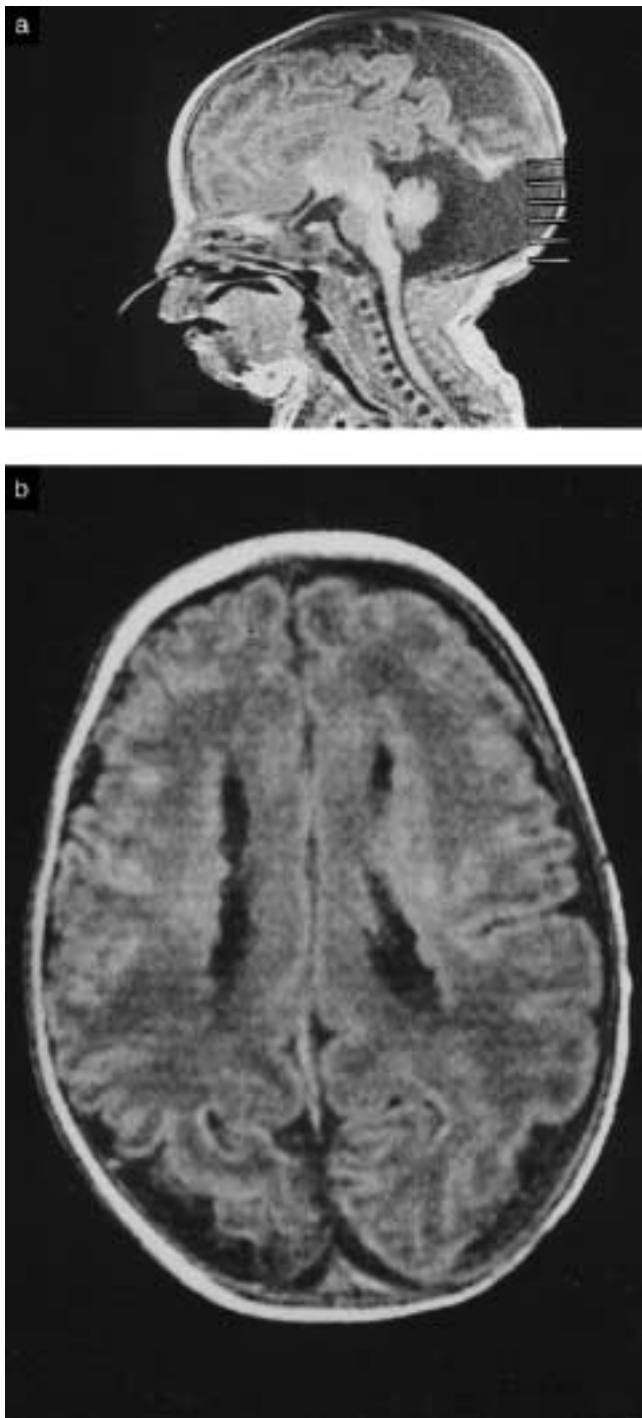


Figure 3 Sagittal magnetic resonance T1-weighted image (a) of the neonatal brain confirming the mega cisterna magna. Axial magnetic resonance T1-weighted image (b) of the neonatal brain at the same level as in Figure 2b demonstrating the subependymal nodular heterotopia.

Affected males have been reported to have more severe neurological and cardiovascular alterations than females and have been found to have other abnormalities such as syndactyly and frontonasal malformation^{11,12}. In our case, cryptorchidism was found to be present in the male neonate.

Eksioglu *et al.*⁹ located a bilateral PNH gene on chromosome Xq28. This gene encodes a protein called filamin-I. This protein is related to the cross-linking of intracellular actin

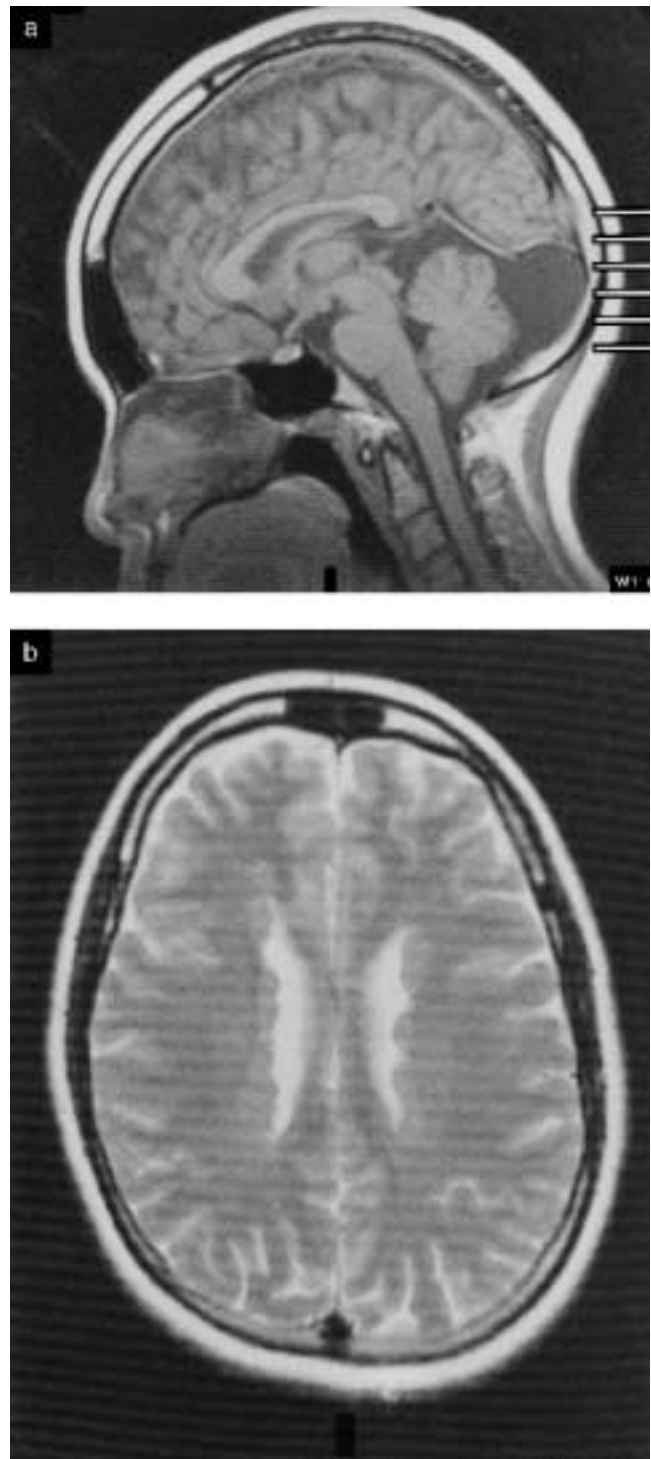


Figure 4 Sagittal magnetic resonance T1-weighted image (a) and axial magnetic resonance T2-weighted image (b) of the mother's brain showing findings similar to those in the fetus. In (a) a mega cisterna magna bulging into the cerebellum and the calvaria is visible with no other posterior fossa anomaly. In (b) an irregular ventricular wall due to the gray matter nodular heterotopia is visible.

which is necessary for cell migration and has other important roles in the vascular and immune systems⁸.

Prenatal PNH is not easily recognized by fetal ultrasound. Between the third trimester and birth, hyperechoic periventricular nodules can be observed¹³ but in the first and early

second trimesters the germinal matrix, also a hyperechoic structure and located in the periventricular area, prevents the visualization of nodular heterotopia. The germinal matrix increases in volume between 8 and 26 weeks of gestation and after that it shrinks until it has almost disappeared by birth.

Fetal MRI studies can help to distinguish between germinal matrix and nodular heterotopia. In the past, fetal movement was a major obstacle in MRI acquisition, but this has been overcome by the development of fast sequences such as T2-weighted half Fourier single shot fast spin echo images. In fetal MRI, nodular heterotopia has been described as being slightly more hypointense than the adjacent germinal matrix but sometimes the difference can be very subtle. Normally, it is the bulging in the lateral ventricular wall that suggests the possibility of PNH. The differential diagnosis of the MRI and sonographic findings includes nodular hamartomas present in tuberous sclerosis although it can be very difficult to differentiate these two entities by prenatal imaging, and a detailed medical family history is required to assist in the diagnosis. Bronshtein *et al.*¹⁴, in a recent letter, suggested that when assessing a fetal anomaly of uncertain significance, examination of the asymptomatic parents may help in the diagnosis and our case corroborates this statement.

The presence of mega cisterna magna has been associated with different central nervous system malformations. A cisterna magna > 10 mm in size between 21 and 28 postmenstrual weeks¹⁵ can suggest more complex abnormalities¹⁶. There is a large variability in the size of the pathological cisterna magna in the last weeks of gestation¹⁷.

The association of posterior fossa malformation with bilateral PNH is not rare and can suggest the diagnosis. Mega-cisterna magna is by far the most frequent anomaly that has been reported in association with bilateral PNH^{1,3,5}.

In conclusion, bilateral subependymal heterotopia can be associated with mega cisterna magna. Fetal MRI can help in the discrimination between the germinal matrix and nodular heterotopia, but a search of the family history is necessary to ascertain the diagnosis of bilateral PNH. It is important to remember that some females will not have a clinical history of seizures and so neuroradiological studies of the mother should be performed in order to confirm the diagnosis.

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