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Prenatal presentation of pyruvate dehydrogenase complex deficiency

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Abstract

We present the case of a female infant referred for prenatal MR evaluation of ventriculomegaly, which had been attributed by the referring obstetrician to aqueductal stenosis. Fetal MR confirmed ventriculomegaly but also demonstrated cerebral volume loss and white matter abnormalities. After birth, the infant developed persistent lactic acidosis. A diagnosis of pyruvate dehydrogenase complex deficiency was made on the basis of metabolic and molecular genetic studies. Ventriculomegaly is a common referral reason for fetal MR, yet there are few published reports of the radiographic findings that accompany inborn errors of metabolism, one potentially under-recognized cause of enlarged ventricles. This case contributes to this small body of literature on the imaging features of pyruvate dehydrogenase complex deficiency by describing preand postnatal MR findings and key clinical details. Our report emphasizes the necessity of considering pyruvate dehydrogenase complex deficiency and other metabolic disorders as potential etiologies for fetal ventriculomegaly since prompt diagnosis may allow for early initiation of treatment and improve outcome.

Keywords

Brain; Fetus; Magnetic resonance imaging; Pyruvate dehydrogenase complex deficiency; Ventriculomegaly

Introduction

Pyruvate dehydrogenase complex deficiency is a rare inborn error of metabolism that typically presents in infancy or early childhood. The enzymatic pyruvate dehydrogenase complex converts pyruvate into acetyl-CoA, which can then enter the Krebs cycle; a defect in this pathway results in conversion of pyruvate into lactic acid instead. Affected individuals usually exhibit progressive neurological deterioration, often accompanied by encephalopathy, seizures and death during infancy or childhood. Characteristic laboratory

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Conflicts of interest None

findings include persistent lactic acidosis [1]. Early recognition and evaluation for this disorder are imperative as carbohydrate restriction or ketogenic diet may improve neurological outcomes [2].

Imaging findings reported in infants and children with pyruvate dehydrogenase complex deficiency include structural brain alterations (partial or complete dysgenesis of the corpus callosum, brainstem and cerebellar hypoplasia, immature sulcation pattern, and neuronal migrational anomalies, including polymicrogyria and grey matter heterotopia) as well as changes attributable to ongoing metabolic injury (progressive ventriculomegaly, cerebral atrophy and global white matter volume loss) [3–6]. Proton MR spectroscopy has been reported to reveal a large lactate doublet at 1.33 ppm, as well as a unique singlet peak at 2.37 ppm reflecting elevated pyruvate [6]. The fetal MR manifestations of pyruvate dehydrogenase complex deficiency have been described only rarely. Reported fetal imaging findings are similar to those seen in infants and include ventriculomegaly, abnormal sulcation patterns as well as brainstem and cerebellar hypoplasia [3, 4, 6]. Periventricular white matter mineralization was also identified by US in one case [3].

We report a patient whose mother was initially referred to a prenatal diagnosis clinic for fetal ventriculomegaly attributed to aqueductal stenosis, but who was found after birth to have pyruvate dehydrogenase complex deficiency. This report provides detailed clinical, prenatal and postnatal imaging findings and considers a differential diagnosis for similar cases that might be encountered.

Case report

A 27-year-old G1P0 presented to a pediatric hospital-affiliated prenatal clinic for further assessment of ventriculomegaly, which had been attributed to congenital aqueductal stenosis by the referring obstetrician. The pregnancy had been unre-markable in the first trimester, with normal maternal prenatal laboratory assessment. Initial second trimester fetal US showed mild ventriculomegaly (11 mm), which had progressed to 17 mm in a follow-up US performed 2 weeks later (Fig. 1). Fetal head circumference measurements lagged 3 weeks behind expected (2nd percentile at 25 weeks' gestational age). Fetal MR imaging performed on a 1.5-T magnet at 32 and 2/7 weeks' gestation confirmed moderate ventriculomegaly, but also demonstrated severe cerebral volume loss (based on thinning of the cerebral tissue and non-effaced extra-axial cerebrospinal fluid spaces in the setting of ventriculomegaly), an immature cerebral sulcation pattern with focal areas of suspected polymicrogyria and patchy hyperintense T2-weighted signal in the white matter (Fig. 2). Of note, cerebellar hemispheres and vermis showed normal development. The corpus callosum was at least partially present but appeared thin. Diffusion-weighted imaging was normal. MR spectroscopy was not performed.

Based on the lagging head growth and evidence of white matter injury, ventriculomegaly was regarded as an ex vacuo phenomenon rather than a consequence of cerebrospinal fluid obstruction. Due to the constellation of imaging findings, congenital cytomegalovirus or another transplacental infection was considered a strong diagnostic possibility. Genetic abnormalities including Aicardi-Goutieres syndrome, cystic leukoencephalopathy without

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megalocephaly and metabolic disorders were considered as well. Recommendations at the prenatal consultation included prenatal laboratory evaluation for congenital infection, MRI after birth and a postnatal work-up that could include screening or targeted genetic testing as directed by the results of the prenatal work-up, examination findings, postnatal MRI and clinical course.

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Prenatal infectious work-up was unrevealing, and the pregnancy continued without additional complications although fetal ventriculomegaly progressed. At 39 weeks, the patient was born by elective cesarean section and was noted to be pale, hypotonic and intermittently apneic, requiring intubation in the delivery room. The infant was small for gestational age, with a birth weight of 2.63 kg (6th percentile). Head circumference was also small, measuring 32 cm (5th percentile). Cord blood was sent for cytomegalovirus polymerase chain reaction and chromosomal microarray, both of which were unrevealing.

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During the first week of the girl's neonatal intensive care unit admission, neurological examination was significant for encephalopathy and axial hypotonia, with increased appendicular tone and increased deep tendon reflexes. Electroencephalography confirmed mild to moderate encephalopathy, with several purely electrographic seizures emanating from the right posterior head region. Postnatal MR, obtained in the first week of life, redemonstrated ex vacuo dilatation of the ventricles with cerebral atrophy and periventricular cystic leukomalacia (Fig. 3). Partial dysplasia of the corpus callosum was also observed (Fig. 3).

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Suspicion for an inborn error of metabolism arose early in her clinical course because of persistent lactic acidosis. Lactate and pyruvate levels were obtained and the resulting lactate-to-pyruvate ratio of 8.8:1 (normal > 10:1 with > 20:1 suggesting mitochondrial disease), in conjunction with MRI findings, raised specific consideration for pyruvate dehydrogenase complex deficiency. Additional metabolic studies, including leukocyte pyruvate dehydrogenase enzymatic testing, were all within normal limits. Due to ongoing clinical concern, the infant was started empirically on a carbohydrate-restricted diet and genes associated with pyruvate dehydrogenase complex deficiency were sent for sequencing. After hospital discharge, genetic testing confirmed the diagnosis of pyruvate dehydrogenase complex deficiency by detecting a pathogenic heterozygous mutation in *PDHA1*.

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At 12 months of age, the child remains on a carbohydrate-restricted diet, with overall improvement in lactate levels. She is microcephalic, with head circumference measuring approximately 3.5 standard deviations below the mean for her age. Developmentally, she is delayed, with slowly improving head control, but she cannot reach for objects and requires physical and occupational therapy. She is able to make vocalizations and is fed nearly entirely by gastrostomy tube. She has sensorineural hearing loss and there is concern for cortical visual impairment. She has not had any further seizures clinically or on electroencephalogram, and her anticonvulsant medication has been discontinued.

Discussion

Ventriculomegaly detected on prenatal US is a common indication for further assessment with fetal MR imaging. This may help identify an apparent point of cerebrospinal fluid obstruction such as the cerebral aqueduct or the posterior fossa [7]. The ex vacuo nature of fetal ventricular enlargement may also be more readily apparent on MR than on US, as in this case. Fetal MR can demonstrate evidence of other intracranial pathology such as neoplasm, hemorrhage or infection. It may also provide clues to an inborn error of metabolism such as pyruvate dehydrogenase complex deficiency. We present the case of an infant referred for prenatal MR evaluation of ventriculomegaly, who was subsequently found to have pyruvate dehydrogenase complex deficiency, a severe inborn error of metabolism.

When ventriculomegaly is detected on fetal imaging, additional findings of microcephaly and marked white matter signal abnormalities direct the differential diagnosis to etiologies explaining either brain parenchymal injury or underdevelopment. When the prenatal health care team is confronted with evidence of small fetal brain size and thin cortex (as opposed to abnormally thick cortex due to a diffuse neuronal migrational anomaly), genetic and environmental causes must be considered [7]. Genetic causes include chromosomal aneuploidy, gene deletion conditions and syndromes such as Smith-Lemli-Opitz, Cornelia de Lange, and Feingold syndromes. Environmental causes include toxic exposures, maternal diabetes, hypoxic injury, placental insufficiency and intrauterine infection [7].

Periventricular white matter cystic abnormalities, particularly when bilateral and multifocal, point to a genetic anomaly or congenital infection. Subependymal cysts may be caused by vascular insults, toxic exposures, infection (particularly rubella or cytomegalovirus), chromosomal anomalies or metabolic abnormalities [7]. Genetic disorders that may manifest with subependymal cysts include Aicardi-Goutieres syndrome, as was considered in this case, with imaging features mimicking viral infection. Metabolic disorders to consider include Zellweger syndrome, congenital disorders of glycosylation, mitochondrial disorders and organic acidurias.

Consideration of a metabolic abnormality affecting fetal brain development may prompt fetal proton MR spectroscopy. Due to fetal motion, this technique can be quite challenging. Furthermore, reports of normal gestation-based MR spectra have yet to be published. Robinson et al. [3] proposed that elevated levels of lactate may not be identified prenatally using MR spectroscopy, since the placental–maternal circulation efficiently removes any excess lactate in the prenatal period. Supporting this speculation, umbilical cord blood lactate levels were normal in their published case of a twin pregnancy, even in the affected infant.

Our case emphasizes the importance of including pyruvate dehydrogenase complex deficiency and other inborn errors of metabolism in the differential diagnosis of fetal ventriculomegaly, especially when parenchymal volume loss and periventricular white matter T2-weighted hyperintensity are seen. Although a definitive diagnosis cannot be made based on these prenatal brain findings alone, antenatal counseling and consideration of this diagnosis could allow for assessment of lactic acidosis in the immediate postnatal period and

initiation of therapy with restricted carbohydrates or ketogenic diet early in the neonatal course, thereby potentially improving outcome.

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Fig. 1.

Prenatal sonography shows ventriculomegaly. Transverse US image through the fetal head at 30 weeks' gestational age shows abnormally enlarged lateral and third (*) ventricles. (Calipers mark far-field lateral ventricle size.) Note also dangling choroid (*arrow*) and simplified sulcation pattern of the cerebral cortex. *Arrowhead* indicates focally abnormally anechoic periventricular white matter, consistent with cystic encephalomalacia, recognized retrospectively. Ventriculomegaly progressed to 25 mm later at 37 weeks' gestational age (not shown here)

Fig. 2.

Prenatal MR imaging performed at 32 2/7 weeks' gestational age. Axial (**a**) and coronal T2-weighted single-shot fast-spin echo (SSFSE) (**b**) at the level of the lateral ventricles shows abnormal ventricular dilatation, correlating with prenatal US. Abnormal patchy areas of abnormally hyperintense T2-weighted periventricular white matter (*white arrows* in **a** and **b**) are more pronounced in the bifrontal lobes than in parietal lobes. Coronal T2 SSFSE sequence (**c**) through the posterior brain shows marked simplification of the cerebral sulcation pattern (*arrowheads*). Note normal morphology of the cerebellum. *LV* lateral ventricle

Fig. 3. Postnatal MR imaging performed at day 6 of life. Axial T1 inversion recovery sequences (**a**, **b**) through the cerebral hemispheres show abnormal enlargement of the lateral ventricles (LV). As seen on prenatal imaging, there is abnormal periventricular leukomalacia (*arrows* in **a**). Cerebral sulcation shows further maturation compared to the fetal brain MRI performed at 32 weeks' gestational age, although sulcation in the bifrontal and bitemporal regions is more developed than in the parietal and occipital regions. Sagittal T1-weighted image through the midline (**c**) shows incomplete formation of the corpus callosum, with only a hypoplastic portion of the anterior body present (*arrow*)