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Expanding the Differential Diagnosis of Fetal Hydrops: An Unusual Prenatal Presentation of Megalencephaly-Capillary Malformation Syndrome

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Research Letter

The megalencephaly-capillary malformation (MCAP) syndrome is a rare disorder characterized by prenatal overgrowth, somatic and cerebral asymmetry, cutaneous vascular malformations, and connective tissues abnormalities.¹ The central nervous system (CNS) and cutaneous manifestations dominate the clinical picture during postnatal life. Structural cardiac, pulmonary, and lymphatic abnormalities are not commonly seen, although two previously reported patients were noted to have fetal hydrops or fetal pleural effusions.² Recently, de novo germline and postzygotic mutations in three genes within the PI3K-AKT signaling pathway (*AKT3*, *PIK3R2*, and *PIK3CA*) were reported to cause a group of related megalencephaly syndromes, including MCAP and the megalencephaly-postaxial polydactyly-polymicrogyria-hydrocephalus (MPPH) syndrome.³

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What is known about this topic? Megalencephaly-capillary malformation (MCAP) syndrome is a rare disorder characterized by growth dysregulation, central nervous system and vascular anomalies, and distal limb malformations. Disruption of PI3K-AKT signaling has recently been implicated as the cause of MCAP.

What does this study add? This study reports a case of MCAP with bilateral pleural effusions and fetal hydrops managed with thoraco-amniotic shunt placement, highlights characteristic features of MCAP that may facilitate prenatal diagnosis, and discusses the possibility of prenatal molecular diagnosis in future cases.

Here, we report a case of MCAP that first came to medical attention at 19 weeks gestation, when a left pleural effusion was identified by routine ultrasonography in 25-year old primigravida. By 22 weeks gestation the effusion had increased in size and became complicated by fetal hydrops. The head circumference (HC) and biparietal diameter were on the 90-95th percentile upon presentation at 22 weeks gestation, and remained so throughout the pregnancy. The cerebral lateral ventricles were asymmetric, but the dimensions were within normal limits for gestational age. No additional structural CNS abnormalities were noted on fetal MRI at 23 6/7 weeks gestation. On echocardiography, normal cardiac structures but mild-to-moderate tricuspid valve regurgitation were observed. No other structural fetal malformations were identified. Amniocentesis and thoracentesis were performed. A male karyotype and normal male pattern on prenatal SNP array were reported. Analysis of the pleural effusion fluid was consistent with a chylothorax. A comprehensive sequencing array for Noonan, LEOPARD, Cardio-Facio-Cutaneous, and Costello Syndrome were reported as negative. Routine prenatal labs, and maternal past medical, social, and family history were non-contributory. Because of rapid re-accumulation of pleural fluid and fetal hydrops, a thoracoamniotic shunt was placed at 23 3/7 weeks gestation. Repeat ultrasounds were performed at 24 2/7, 31 4/7, and 35 6/7 weeks gestation at our center, and weekly in the primary obstetrician's office. There was near-complete resolution of the pleural effusion and fetal hydrops, and the pregnancy went on uncomplicated. Induction of labor was initiated at 39 5/7 weeks gestation and due to fetal distress, a Cesarean delivery was performed. Birth-weight was 3890g (75th percentile), length 53cm (75th percentile), head circumference (HC) 38.5cm (97th percentile) and the APGARs were 7 at 1 minute and 8 at 5 minutes. However, he did require blow-by oxygen in the delivery room, followed by supplemental oxygen via nasal cannula, in order to maintain target oxygen saturations during the first 24 hours of life.

Initial physical exam was notable for macrocephaly, bilateral post-axial polydactyly of the feet, and an extensive capillary malformation seen on the trunk, all four extremities, both sides of the lower portion of the face, chin, lower lip, and midline forehead. (See Figure 1) The rash was relatively light, and had a reticular pattern reminiscent of cutis marmorata. No dysmorphic facial features were noted. Cardiac, pulmonary and neurologic exams were unremarkable and no other abnormalities were identified. Magnetic resonance imaging of the brain demonstrated bilateral perisylvian polymicrogyria (right more extensive than left), with additional involvement of the right frontal lobe, globally prominent medullary veins (right greater than left), and right hemimegalencephaly. Slightly increased signal intensity was seen within the white matter on FLAIR sequences. The patient failed screening brainstem auditory evoked response (BAER) testing bilaterally. The routine electroencephalogram (EEG) performed was unremarkable.

The initial chest radiograph demonstrated coarse interstitial lung markings, but no pleural effusions. The neonate weaned off of nasal cannula during the first day of life, and was allowed to breastfeed. He fed well without any difficulties, and the pleural effusions did not re-accumulate. He remained seizure free through his hospital course, and was discharged home on day of life eight.

Sanger sequencing of the *PIK3CA* gene was performed on DNA obtained from buccal cells, cultured fibroblasts, and DNA extracted directly from skin (the latter two specimens were obtained from the digits surgically removed to correct polydactyly). A heterozygous mutation in *PIK3CA* (c.501G>C, p.R115P) was found in 20% of buccal cells, 25% of skin cells, and none of the cultured fibroblasts. (See Supplemental Figure 1)

A recent comprehensive clinical review of MCAP and related megalencephaly syndromes proposed five major classes of developmental abnormalities seen in these disorders: 1)

megalencephaly and associated growth dysregulation; 2) developmental vascular anomalies; 3) distal limb malformations, including syndactyly and polydactyly; 4) cortical brain malformations; and, 5) a distinctive connective tissue dysplasia.¹ Abnormalities of the central nervous system have the greatest impact on the long-term outcome for these patients. In addition to megalencephaly, ventriculomegaly, hydrocephalus, cerebellar tonsillar ectopia, abnormalities of the corpus callosum, and polymicrogyria are commonly reported features. As a consequence of these structural abnormalities, infantile hypotonia, seizures, developmental delay and intellectual disabilities, and behavioral problems are common. In some individuals, the developmental disability may be profound (non-verbal, non-ambulatory).^{1, 4}

The vascular anomalies seen in MCAP are typically cutaneous, but may also involve internal structures. Cutaneous capillary malformations can be found in any location, but midline facial capillary malformations are characteristic.⁵ Cutaneous infantile hemangiomas are seen in a smaller number of individuals. Internal vascular anomalies, including an abdominal hemangioma, vascular rings, and dilated transverse sinuses on MR imaging of the brain have been reported.¹ Structural congenital heart disease, including tetralogy of Fallot, ASD/VSD, cardiomyopathy, and arrhythmias leading to sudden death have rarely been seen.^{4, 6-8}

We are aware of only two previously reported cases in the literature that were affected by hydrops fetalis. In the original description of MCAP by Clayton-Smith, *et al*, Case 6 was noted to have increased fetal growth, polyhydramnios, and hydrops during the third trimester.² The findings of MCAP were recognized immediately after birth, but the baby died on the second day of life due to respiratory failure. Post-mortem examination was notable for bilateral angiomatosis at the apices of both lungs. Case 9 was found to have bilateral pleural effusions during fetal life. These effusions were drained prenatally, allowing the pregnancy to progress to 38 weeks gestation. Other stigmata suggestive of MCAP were noted after birth. No mention is made of subsequent cardiopulmonary difficulties. These cases highlight the potentially life-saving role for thoracoamniotic shunt placement in this particular presentation. The wide range of neurodevelopmental outcomes should be considered and discussed with families if a prenatal diagnosis of MCAP is made, prior to proceeding with aggressive fetal management.

The current case, combined with those previously reported by Clayton-Smith, *et al*, suggest that on evaluation of a fetus with non-immune hydrops one should also consider megalencephaly-capillary malformation (MCAP) syndrome in the differential diagnosis. Additional diagnostic clues evident by prenatal ultrasonography that may prompt consideration of this diagnosis include megalencephaly with or without other structural CNS abnormalities, somatic overgrowth or asymmetry, and distal limb anomalies. The recent identification of mutations in *AKT3*, *PIK3R2*, and *PIK3CA* as the cause of MCAP now also opens the possibility of obtaining a molecular diagnosis prenatally.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

A relatively light, but extensive reticulated capillary malformation is evident on the arms, legs, trunk, and lower portion of the face. The right limbs are similarly involved, but to a lesser extent.