Child Neurology: Cortical Malformations in Preterm Infants: Case From a Prospective Cohort

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Abstract:

Malformations of cortical development (MCD) are a rare group of disorders with heterogeneous clinical, neuroimaging, and genetic features. MCDs consist of disruptions in the development of the cerebral cortex secondary to genetic, metabolic, infectious or vascular etiologies. MCDs are typically classified by stage of disrupted cortical development as secondary abnormal: (1) neuronal proliferation or apoptosis, (2) neuronal migration, or (3) postmigrational cortical development. MCDs are typically detected with brain magnetic resonance imaging (MRI) when an infant or child becomes symptomatic, presenting with seizures, developmental delay, or cerebral palsy. With recent advances in neuroimaging, cortical malformations can be detected using ultrasound or MRI during the fetal period, or in the neonatal period. Interestingly, preterm infants are born at a time when many cortical developmental processes are still occurring. However, there is a paucity of literature describing the neonatal imaging findings, clinical presentation, and evolution over time of cortical malformations in preterm infants. Here, we present the neuroimaging findings from early life to term-equivalent age as well as childhood neurodevelopmental outcomes of an infant born very preterm (<32 weeks’ post-menstrual age) with MCD detected incidentally on neonatal research brain MRI. These brain MRIs were performed as part of a prospective longitudinal cohort study of 160 very preterm infants; MCDs were detected incidentally in two infants.

Case:

This is a case of a male neonate with a MCD detected incidentally on research MRI from a prospective cohort of 160 infants born very preterm. Two infants had MCDs (1.3%, 95% CI 0.2-4.4%) detected incidentally on research MRIs. The prospective cohort study was approved by the
A male neonate was born at 28+5 weeks post-menstrual age (PMA) by cesarean section to a 38-year-old mother who presented with preterm labor. The pregnancy was complicated by an episode of bacterial vaginosis and a shortened cervix. Antenatal ultrasound showed no brain abnormalities. Placental pathology revealed a morbidly adherent placenta and marginal insertion of the umbilical cord. At birth, the baby required intubation. Apgar scores were 1 and 5 at 1 and 5 minutes, respectively. His birth weight was 1195g (52nd percentile for gestational age (GA)) and his head circumference was 28cm (88th percentile for GA). His neonatal course was unremarkable except for episodes of apnea/bradycardia, managed with non-invasive ventilation. He exhibited a normal neurological examination throughout his admission. His first head ultrasound, on day of life 2 (at 29 weeks PMA), was suspicious for early ischemic changes in the right anterior brain and bilateral occipital areas. Subsequent head ultrasounds were normal. Two research brain MRIs were conducted in the neonatal period. His first brain MRI was performed at 32+1 weeks PMA and showed periventricular nodular heterotopia in the right temporal and occipital regions associated with right frontal transmantle dysplasia and polymicrogyria (Figure, A and B). A second brain MRI at 45+2 weeks PMA confirmed the presence of multiple foci of periventricular nodular heterotopia in the right occipital and temporal horns and better characterized the cortical malformation as right frontal closed-lip schizencephaly (Figure, C and D). Genetic investigations revealed a normal microarray and heterozygous variants of unknown
significance in the LAMC3 and WDR62 genes on a brain malformation gene panel. Although mutations in these genes are associated with MCD, inheritance is autosomal recessive, thus they did not explain the brain MRI findings. Neurodevelopmental outcomes were assessed longitudinally up to a corrected age of 5-years. At 18 months, he presented with a normal neurological examination and neurodevelopmental scores, assessed with Bayley Scales of Infant and Toddler Development-III (Bayley-III). At 36 months, his cognitive and language performance were both in the lower range of normal (Bayley-III Cognitive score 85, Bayley-III Language score 86), and his motor score was within the normal range (Bayley-III Motor score 94). At 5 years, he exhibited a normal neurological exam, a normal cognitive assessment based on the Wechsler Primary and Preschool Scale of Intelligence (WPPSI), 4th edition Full Scale IQ (composite score 92, 30th percentile) and a normal motor performance based on the Movement Assessment Battery for Children, 2nd edition (M-ABC2) (total score 69, 25th percentile).

Discussion:
We report the imaging findings and neurodevelopmental outcomes of an infant born very preterm with MCD that was detected incidentally on research neonatal brain MRIs. Overall, MCDs were detected incidentally in two infants from a larger prospective cohort study of 160 children born very preterm enrolled from two neonatal intensive care units of one city; the other child with incidental findings was lost to follow-up. This case illustrates the neuroimaging evolution of an MCD from early-life to term-equivalent age. Early brain ultrasounds in preterm infants may be useful in screening for brain injury, however this report demonstrates the complementary role of brain MRI in detecting brain malformations. Detecting MCDs and other
Brain malformations early allow for appropriate investigations and close neurodevelopmental follow-up.

Very preterm infants are born during a period of rapid brain maturation and growth, when many cortical developmental processes are still occurring. There are three main stages of cortical development: neuronal proliferation in the ventricular zone (peak between weeks 9 and 12 of gestation), migration of neurons to the developing cortex (peak between weeks 13 and 18 of gestation), and post-migrational processes including cortical organization and development of neuronal connectivity (begins around 17 weeks of gestation and continues for years postnatally) (Table).1-4 It is important to note that disruptions in early stages of cortical development can affect subsequent stages as many cortical developmental processes occur simultaneously. Different brain regions also undergo cortical development at different periods of time.2, 5 Further, the same genes can regulate processes occurring at different stages of cortical development.2, 5, 6 Thus, MCDs may present as a combination of multiple cortical malformations and are often associated with other brain malformations.5 For example, the reported case presents a combination of MCDs with malformations of neuronal migration (periventricular nodular heterotopia) and post-migrational cortical developmental disorders (closed-lip schizencephaly).

Abnormalities in cortical structural development are now increasingly recognized in children born preterm.7 In preterm infants, there is an increased potential for disruption of cortical developmental processes during the prenatal, perinatal and postnatal periods. This increased potential for disruption may be secondary to obstetric complications or neonatal clinical instability which can result in ischemic brain injury. Importantly, an association between brain
malformations, including MCDs, and preterm birth has been reported. Thus, although rare, MCDs are an important differential to consider in preterm infants with atypical neurodevelopmental trajectories, focal neurologic abnormalities, or focal seizures.

With recent advances in neuroimaging, MCD can be detected antenatally with ultrasound or MRI. However, for the patient described, antenatal ultrasound performed as part of routine antenatal care in the early second trimester was normal. An early postnatal clinical head ultrasound, performed as part of routine neonatal screening in Canada to detect preterm brain injury (intraventricular hemorrhage and periventricular leukomalacia), in this infant revealed early ischemic changes. Subsequently, MCDs were detected on the child’s research MRI, following which he was referred to clinical genetics and neurology for further investigations and management. Head ultrasound can also be useful in looking for signs of brain malformations or associated features such as the presence of calcifications or ventriculomegaly. However, brain changes in MCDs can be subtle and brain MRI offers better characterization of the cortical anomalies along with any associated brain malformations and prematurity-related brain changes that may be missed by ultrasound. Thus, the recommended neuroimaging modality for characterizing atypical head ultrasound findings and detecting MCDs is brain MRI.

The appearance of MCDs may become more conspicuous over time. This neuroimaging evolution of MCD over time was demonstrated by Inder et al. in their case report of a very preterm infant with minor abnormalities in the perisylvian regions noted on MRI at 31 weeks PMA, followed by extensive bilateral perisylvian polymicrogyria observed on MRI at 3 months corrected age. In that case, an underlying ischemic etiology was suspected given the
simultaneous presence of extensive bilateral cystic periventricular leukomalacia in the infant.\textsuperscript{14} Interestingly, similar to the case reported by Inder et al., we report evolution of imaging findings between brain MRIs performed early in life and at term equivalent age in our patient, for whom we suspect an ischemic underlying cause. Indeed, our hypothesis is that this preterm neonate suffered from an ischemic brain injury, probably around the time of birth, that subsequently altered cortical development. This hypothesis is supported by the early ischemic changes detected on head ultrasound (on day of life 2), the presence of unilateral MCDs and evolution on neuroimaging. Detection of MCDs can depend on timing of the MRI as the long-lasting consequences of early ischemic injury can evolve over time. Additionally, ongoing myelination alters the appearance of the grey-white matter junction.\textsuperscript{2} It is easiest to differentiate cortex from white matter, and MCDs, before myelination begins (neonatal period) or after myelination is complete (after 2-3 years of age) as contrast between cortex and white matter decreases during myelination.\textsuperscript{2, 15} Thus, it may be necessary to repeat neuroimaging studies after completion of myelination in patients with a high suspicion for MCDs.

This paper reports the neuroimaging findings and neurodevelopmental trajectory of a child born very preterm with MCD detected incidentally on neonatal brain MRIs. The clinical relevance of this case includes the complementary role of brain MRI detecting MCD in a preterm infant with suspicious findings on neonatal head ultrasounds. The neuroimaging evolution over the neonatal period underlines that brain development is dynamic, with ongoing changes in the postnatal period. During this crucial period for brain development, cortical developmental processes may be altered by various mechanisms, including ischemic injury, and result in MCD. Thus, in cases of suspicious head ultrasound findings, neuroimaging with brain MRI is indicated to detect
MCD, and could be repeated around 2 years of age after myelination is complete to understand the full extent of the MCD. Finally, this case highlights the importance of having a broad differential for brain abnormalities in infants born very preterm, which includes MCD in addition to brain injury.

Table. Stages of cortical development and examples of cortical malformations that occur as a result of abnormalities at each stage.

<table>
<thead>
<tr>
<th>Stage of cortical development</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferation and apoptosis</td>
<td>Macrocephaly, microcephaly, hemimegalencephaly</td>
</tr>
<tr>
<td>Neuronal migration</td>
<td>Periventricular nodular heterotopia, subcortical band heterotopia, lissencephaly</td>
</tr>
<tr>
<td>Postmigrational cortical development</td>
<td>Focal cortical dysplasia, polymicrogyria, schizencephaly</td>
</tr>
</tbody>
</table>

Adapted from 2, 5
Figure: Right frontal schizencephaly and periventricular nodular heterotopia in very preterm infant.

T2-weighted non-contrast sagittal and axial sequences acquired at 32+1 weeks PMA (A and B) and 45+2 weeks PMA (C and D) showing right frontal closed-lip schizencephaly (yellow arrows) and periventricular nodular heterotopia along the posterior horn of the right lateral ventricle (red arrows). T2-weighted sequences were acquired using a similar protocol to those acquired as part of clinical neonatal MRI.
References:

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