Child Neurology: Cortical Malformations in Preterm Infants

Case From a Prospective Cohort

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Neurology® 2023;101:235-238. doi:10.1212/WNL.0000000000207265

Abstract

Malformations of cortical development (MCD) are a rare group of disorders with heterogeneous clinical, neuroimaging, and genetic features. MCD consist of disruptions in the development of the cerebral cortex secondary to genetic, metabolic, infectious, or vascular etiologies. MCD are typically classified by stage of disrupted cortical development as secondary to abnormal: (1) neuronal proliferation or apoptosis, (2) neuronal migration, or (3) post-migrational cortical development. MCD are typically detected with brain 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. Of interest, 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. In this study, we present the neuroimaging findings from early life to term-equivalent age and childhood neurodevelopmental outcomes of an infant born very preterm (<32 weeks' postmenstrual 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; MCD were detected incidentally in 2 infants.

Case

This is a case of a male neonate with MCD detected incidentally on research MRI from a prospective cohort of 160 infants born very preterm. Two infants had MCD (1.3%, 95% CI 0.2–4.4) detected incidentally on research MRIs. The prospective cohort study was approved by the Research Ethics Board at the Hospital for Sick Children and Mount Sinai Hospital. Written informed consent was obtained for all participants in the cohort; further written informed consent was obtained from the parents of the child described in more detail specifically for this case report.

A male neonate was born at 28 + 5 weeks postmenstrual 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 1195 g (52nd percentile for gestational age [GA]), and his head circumference was 28 cm (88th percentile for GA). His neonatal course was unremarkable except for episodes of apnea/bradycardia, managed with noninvasive ventilation. He exhibited a normal neurological examination throughout his admission. His first

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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 variations 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 the age of 5 years, he exhibited a normal neurological examination, 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, MCD were detected incidentally in 2 infants from a larger prospective cohort study of 160 children born very preterm enrolled from 2 neonatal intensive care units of 1 city; the other child with incidental findings was lost to follow-up. This case illustrates the neuroimaging evolution of 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 MCD and other brain malformations early allow for appropriate investigations and close neurodevelopmental follow-up.

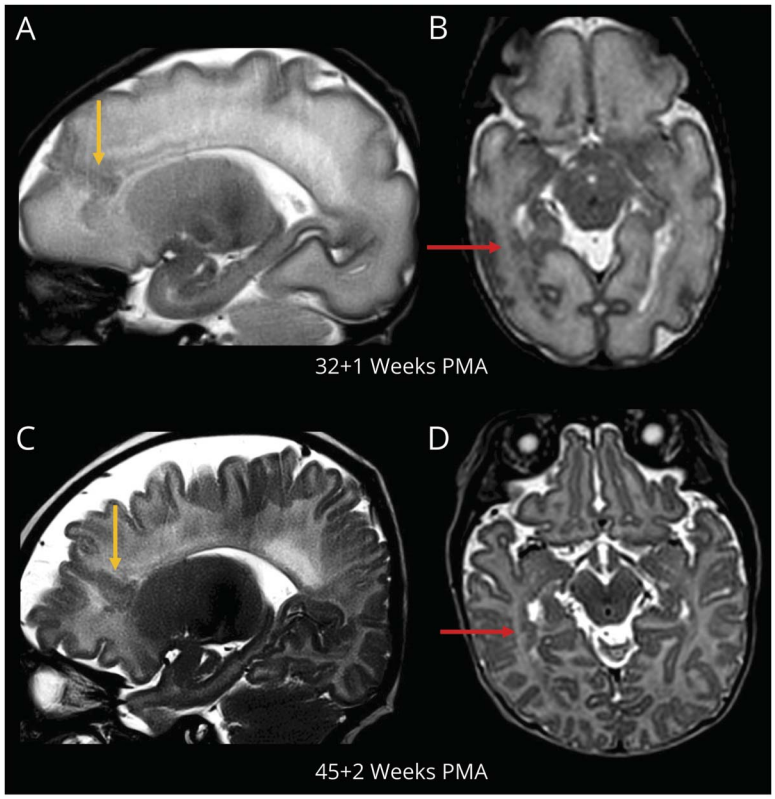
Very preterm infants are born during a period of rapid brain maturation and growth, when many cortical developmental processes are still occurring. There are 3 main stages of cortical development: neuronal proliferation in the ventricular zone (peak between weeks 9 and 12 of gestation), migration of neurons to the developing cortex (peak between weeks 13 and 18 of gestation), and postmigrational processes including cortical organization and development of neuronal connectivity (begins at approximately 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 because many cortical developmental processes occur simultaneously. Different brain regions also undergo cortical development at different periods.[2,5] Furthermore, the same genes can regulate processes occurring at different stages of cortical development.[2,5,6] Thus, MCD 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 MCD with malformations of neuronal migration (periventricular nodular heterotopia) and postmigrational 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. Of importance, an association between brain malformations, including MCD, and preterm birth has been reported.[8] Thus, although rare, MCD 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.[9,10] 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),[11] in this infant revealed early ischemic changes. Subsequently, MCD were detected on the child's research MRI, after 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.[12] However, brain changes in MCD 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.[2,13] Thus, the recommended neuroimaging modality for characterizing atypical head ultrasound findings and detecting MCD is brain MRI.

The appearance of MCD may become more conspicuous over time. This neuroimaging evolution of MCD over time was previously demonstrated in a case report of a very preterm infant with minor abnormalities in the perisylvian regions

Figure Right Frontal Schizencephaly and Periventricular Nodular Heterotopia in a Very Preterm Infant



T2-weighted noncontrast 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

noted on MRI at 31 weeks PMA, followed by extensive bilateral perisylvian polymicrogyria observed on MRI at 3 months corrected age.[14] In that case, an underlying ischemic etiology was suspected, given the simultaneous presence of extensive bilateral cystic periventricular leukomalacia in the infant. Of interest, similar to that case, we report the 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 experienced an ischemic brain injury, probably during birth, which 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 MCD and evolution on neuroimaging. Detection of MCD can depend on timing of the MRI because the long-lasting consequences of early ischemic injury can evolve over time. In addition, ongoing myelination alters the appearance of the gray-white matter junction.[2] It is easiest to differentiate cortex from white matter, and MCD, before myelination begins (neonatal period) or after myelination is complete (after 2–3 years of age) because contrast between cortex and white matter decreases during myelination.[2,15] Thus, it may be necessary to repeat neuroimaging studies after completion of myelination in patients with a high suspicion for MCD.

This study 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

Table Stages of Cortical Development and Examples of Cortical Malformations That Occur Because of Abnormalities at Each Stage [2,5]

Stage of cortical development	Examples
Proliferation and apoptosis	Macrocephaly, microcephaly, and hemimegalencephaly
Neuronal migration	Periventricular nodular heterotopia, subcortical band heterotopia, and lissencephaly
Postmigrational cortical development	Focal cortical dysplasia, polymicrogyria, and schizencephaly

findings, neuroimaging with brain MRI is indicated to detect MCD and could be repeated at approximately 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.

Acknowledgment

The authors thank the children and families who participated in the longitudinal study. The authors also thank Giselle Da Rocha, Mark LePine, Jessie Guo, Stephanie Au-Young, and the staff in the Neonatal Follow-up Program at Mount Sinai Hospital for their assistance with this study.

Study Funding

Canadian Institutes for Heath Research (MOP-136966 and PJT-168894); Brain Canada (The Canadian Neonatal Brain Platform); Cerebral Palsy Alliance (PG-016817).

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* October 27, 2022. Accepted in final form February 21, 2023. Submitted and externally peer reviewed. The handling editor was Resident & Fellow Section Deputy Editor Ariel Lyons-Warren, MD, PhD.

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References

1. Bystron I, Blakemore C, Rakic P. Development of the human cerebral cortex: Boulder Committee revisited. *Nat Rev Neurosci.* 2008;9(2):110-122. doi. 10.1038/nrn2252
2. Severino M, Geraldo AF, Utz N, et al. Definitions and classification of malformations of cortical development: practical guidelines. *Brain*. 2020;143(10):2874-2894. doi. 10.1093/brain/awaa174
3. Raybaud C, Widjaja E. Development and dysgenesis of the cerebral cortex: malformations of cortical development. *Neuroimaging Clin N Am.* 2011;21(3):483-543.
4. Budday S, Steinmann P, Kuhl E. Physical biology of human brain development. *Front Cel Neurosci.* 2015;9:257. doi. 10.3389/fncel.2015.00257
5. Barkovich AJ, Guerrini R, Kuzniecky RI, Jackson GD, Dobyns WB. A developmental and genetic classification for malformations of cortical development: update 2012. *Brain*. 2012;135(5):1348-1369. doi. 10.1093/brain/aws019
6. Barkovich J. Complication begets clarification in classification. *Brain*. 2013;136(2):368-373. doi. 10.1093/brain/awt001
7. Zhang Y, Inder TE, Neil JJ, et al. Cortical structural abnormalities in very preterm children at 7years of age. *NeuroImage*. 2015;109:469-479. doi. 10.1016/j.neuroimage.2015.01.005
8. Brown WR. Association of preterm birth with brain malformations. *Pediatr Res.* 2009;65(6):642-646. doi. 10.1203/pdr.0b013e31819e7422
9. Griffiths PD, Bradburn M, Campbell MJ, et al. Use of MRI in the diagnosis of fetal brain abnormalities in utero (MERIDIAN): a multicentre, prospective cohort study. *Lancet*. 2017;389(10068):538-546. doi. 10.1016/s0140-6736(16)31723-8
10. Griffiths PD, Bradburn M, Campbell MJ, et al. MRI in the diagnosis of fetal developmental brain abnormalities: the MERIDIAN diagnostic accuracy study. *Health Technol Assess.* 2019;23(49):1-144. doi. 10.3310/hta23490
11. Guillot M, Chau V, Lemyre B. Routine imaging of the preterm neonatal brain. *Paediatr Child Health.* 2020;25(4):249-255. doi. 10.1093/pch/pxaa033
12. Leijser LM, de Bruine FT, Steggerda SJ, van der Grond J, Walther FJ, van Wezel-Meijler G. Brain imaging findings in very preterm infants throughout the neonatal period: part I. Incidences and evolution of lesions, comparison between ultrasound and MRI. *Early Hum Dev.* 2009;85(2):101-109. doi. 10.1016/j.earlhumdev.2008.11.010
13. Inder TE, De Vries LS, Ferriero DM, et al. Neuroimaging of the preterm brain: review and recommendations. *J Pediatr*. 2021;237:276-287.e4. doi. 10.1016/j.jpeds.2021.06.014
14. Inder TE, Huppi PS, Zientara GP, et al. The postmigrational development of polymicrogyria documented by magnetic resonance imaging from 31 Weeks' postconceptional age. *Ann Neurol*. 1999;45(6):798-801. doi. 10.1002/1531-8249(199906)45:6<798::aid-ana16>3.0.co;2-u
15. Eltze CM, Chong WK, Bhate S, Harding B, Neville BG, Cross JH. Taylor-type focal cortical dysplasia in infants: some MRI lesions almost disappear with maturation of myelination. *Epilepsia*. 2005;46(12):1988-1992. doi. 10.1111/j.1528-1167.2005.00339.x