CASE REPORT

Four-year follow-up of megalencephaly, polymicrogyria, postaxial polydactyly and hydrocephalus (MPPH) syndrome

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SUMMARY

A male infant was born by emergent caesarean section at 39 weeks gestational age secondary to maternal and fetal distress. Initial physical examination was notable for macrocephaly (greater than +2SD), postaxial polydactyly of the hands and facial dysmorphism. Head imaging demonstrated diffuse polymicrogyria without hydrocephalus. All findings were consistent with a diagnosis of megalencephaly, polymicrogyria, postaxial polydactyly and hydrocephalus (MPPH) syndrome. At the 4-year follow-up, megalencephaly persisted without evidence of hydrocephalus. The child was severely delayed with a stable seizure disorder controlled with dual antiepileptic therapy. This case meets the classic criteria for MPPH syndrome, adding to the limited experience with this disease. The 4-year follow-up and absence of hydrocephalus, once thought to be a key diagnostic criterion, adds to our understanding of the long-term sequelae.

BACKGROUND

Megalencephaly, polymicrogyria, postaxial polydactyly and hydrocephalus (MPPH) syndrome is a rare, relatively newly described disorder that may have overlapping features with other megalencephaly syndromes.¹ Differentiating MPPH from other causes of megalencephaly is important for continued specialty care and follow-up, prognosis and developmental support for affected individuals and their families. Follow-up reports of individuals affected with MPPH are limited.

CASE PRESENTATION

A 4-year-old boy is the fifth child born to non-consanguineous Somali parents. The family history was significant for an older sibling with cerebral palsy and one prior maternal miscarriage. The infant was born in the USA and received appropriate prenatal care. Prenatal ultrasonography at 28 weeks gestation showed dilated frontal, third and lateral cerebral ventricles. At 39 weeks gestation, the infant was delivered by emergent-caesarean section for maternal and fetal distress. Apgar scores were 1, 5 and 7. The infant required resuscitation with positive pressure ventilation and stimulation. Birth measurements were consistent with an appropriately grown infant with a birth weight of 3910 g (75th percentile for age), length of 53 cm (75th percentile for age) and macrocephaly with occipital-frontal circumference of 40 cm (greater than +2SD). Physical examination was significant for bilateral postaxial

polydactyly of both hands and mildly decreased tone throughout. Facial dysmorphism was noted with frontal bossing, low-set ears, a flat nasal bridge and a high-arched palate.

INVESTIGATIONS

The brain MRI showed diffuse polymicrogyria, particularly prominent in the perisylvian regions bilaterally, without evidence of hydrocephalus (figure 1).

Laboratory investigation for an infectious aetiology was negative including viral studies. An echocardiogram and renal ultrasound were unremarkable. Chromosome analysis was normal. Ophthalmological examination was normal and after failing two hearing screens, brainstem auditory evoked responses were also normal.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes MPPH as well as other megalencephaly syndromes, most notably megalencephaly-polymicrogyria-mega-corpus callosum syndrome (MEG-PMG-MegaCC) and

Figure 1 MRI obtained at birth that showed blurring of the grey-white matter junction suggestive of diffuse polymicrogyria. Findings were most prominent in the perisylvian regions bilaterally and stable on repeat head imaging at 4 months, 1 year and 18 months of age.

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macrocephaly-capillary malformation syndrome (M-CM or MCAP). Differentiation depends on clinical and radiographic findings at initial presentation and with on-going surveillance, as some of the features of these diseases may present beyond the newborn period.

This case report is consistent with the core features of MPPH: progressive megalencephaly, polymicrogyria and distal limb anomalies, most commonly postaxial polydactyly.² Secondary features of MPPH include hypotonia, developmental delay and facial dysmorphism—all of which are present in our patient. Seizures were identified in follow-up, also a secondary feature of MPPH. Distinguishing features of M-CM or MCAP, including vascular anomalies, syndactyly and heterotopia are notably absent. Other less frequently observed features of M-CM and MCAP, including somatic overgrowth and asymmetry, and connective tissue dysplasia are also absent.

TREATMENT

No treatment guidelines currently exist for children affected with MPPH. After initial stabilisation and evaluation in the neonatal intensive care unit, the infant was discharged with close follow-up with paediatric neurology, paediatric neurosurgery and their primary care paediatrician. Growth parameters and development were closely monitored and repeat head imaging was performed at regular intervals until 18 months of age.

OUTCOME AND FOLLOW-UP

At 6 months of age, the infant developed left eye deviation and fluttering eyelids. An EEG showed seizures originating in the right occipital lobe and spreading to the ipsilateral temporal lobe. Seizures were eventually controlled with dual antiepileptic therapy. Head imaging at 4 months of age and repeated at 1 year and 18 months of age continued to show stable diffuse polymicrogyria without hydrocephalus. A trial off antiepileptic therapy at 3 years of age resulted in return of multiple daily seizures and drop attacks. Dual antiepileptic therapy was reinstituted, with improved seizure control. At 4 years of age, the head circumference continued to track greater than +2SD from mean (figures 2 and 3). Weight, height and body mass index were within the normal range for age. Development was severely delayed. The child was non-verbal and unable to follow

simple commands. Mild central hypotonia persisted, resulting in delayed walking and an unsteady gait.

DISCUSSION

MPPH was first described by Mirzaa *et al*¹ in 2004 in a series of five unrelated children, ages 6 months to 8 years of age. This constellation of findings was again described in several subsequent small or single case reports.^{3–8} The defining characteristics of this syndrome have been debated due to overlap with other syndromes of macrocephaly, most notably MEG-PMG-MegaCC and M-CM or MCAP.⁹ Mirzaa *et al* recently published a comprehensive review of MCAP and MPPH in an effort to delineate the unique characteristics of these rare, newly identified and overlapping syndromes. Data continue to suggest that MPPH is a distinct syndrome, but with overlapping features that may suggest a commonly affected biological pathway.² Depending on the diagnostic criteria used, between 12 and 19 cases of MPPH have been described in the literature to date.

This sporadic syndrome is presumed to be genetic. Two related infants with an 'MPPH-like' phenotype were found to have a common unbalanced translocation resulting in a sub-microscopic chromosome 5q35 deletion, but this finding has not been replicated in other patients with MPPH.¹⁰ Additionally, a case of MPPH/M-CM with overlapping features was found to have a paternally derived loss of 4q28.3, likely a benign variant.^{9–10} Most recently, exome sequencing in families affected by MPPH or the closely related syndrome MCAP has identified a potential common biological pathway. Mutations in central components of the phosphatidylinositol 3-kinase-AKT pathway were identified in 13/19 patients with MPPH.¹¹ Prior to this finding, a chromosome analyses of the affected patients, including comparative genomic hybridisation (CGH), have been unrevealing. Our patient represents a sporadic case without family history of macrocephaly. Parents had two subsequent children after the birth of this affected child, both with normal development, somatic and head growth. As noted, chromosome analysis was normal. A CGH or further genetic testing was not carried out due to parental preference.

MPPH has been associated with developmental delay ranging from mild to profound. Megalencephaly is often severe and in most cases has required surgical intervention to relieve

Figure 2 Head circumference from birth to 36 months that shows progressive macrocephaly despite the absence of hydrocephalus.

Figure 3 Head circumference from 2 years to current with continued macrocephaly.

presumed hydrocephalus. Interestingly, of the children with MPPH that have had hydrocephalus and subsequent surgical intervention, mild to moderate ventricular enlargement and progressive megalencephaly persisted postoperatively.^{2–9} Tore *et al*⁸ report a child with the core features of MPPH *without* frank hydrocephalus and with normal psychomotor development at 1 year of age despite findings of diffuse polymicrogyria and a seizure disorder. We report an additional case of MPPH *without* hydrocephalus, a child who is significantly affected at 4-year follow-up and exemplifies the heterogeneous phenotype of MPPH.

Learning points

- Megalencephaly, polymicrogyria, postaxial polydactyly and hydrocephalus (MPPH) represents a rare but distinct disorder with overlapping features with other megalencephaly syndromes.
- Ongoing surveillance is necessary to correctly diagnose affected children and to identify and treat common sequelae, although current treatment guidelines are lacking.
- Collective experience suggests that developmental sequelae are heterogeneous, but most often profound.
- Hydrocephalus is not necessary for diagnosis and recent findings question whether surgical intervention is truly beneficial in this select population, although conclusive data is lacking.

Contributors TZ collected data and drafted case report with revisions. KR oversaw revisions and approved final version.

Competing interests None.

Patient consent Obtained.

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REFERENCES

- 1 Mirzaa G, Dodge NN, Glass I, *et al*. Megalencephaly and perisylvian polymicrogyria with postaxial polydactyly and hydrocephalus: a rare brain malformation syndrome associated with mental retardation and seizures. *Neuropediatrics* 2004;35:353–9.
- 2 Mirzaa GM, Conway RL, Gripp KW, *et al*. Megalencephaly-capillary malformation (MCAP) and megalencephaly-polydactyly-polymicrogyria-hydrocephalus (MPPH) syndromes: two closely related disorders of brain overgrowth and abnormal brain and body morphogenesis. *Am J Med Genet A* 2012;158A:269–91.
- 3 Colombani M, Chouchane M, Pitelet G, *et al*. A new case of megalencephaly and perisylvian polymicrogyria with post-axial polydactyly and hydrocephalus: MPPH syndrome. *Eur J Med Genet* 2006;49:466–71.
- 4 Garavelli L, Guareschi E, Errico S, *et al*. Megalencephaly and perisylvian polymicrogyria with postaxial polydactyly and hydrocephalus (MPPH): report of a new case. *Neuropediatrics* 2007;38:200–3.
- 5 Osterling WL, Boyer RS, Hedlund GL, *et al*. MPPH syndrome: two new cases. *Pediatr Neurol* 2011;44:370–3.
- 6 Pisano T, Meloni M, Cianchetti C, *et al*. Megalencephaly, polymicrogyria, and hydrocephalus (MPPH) syndrome: a new case with syndactyly. *J Child Neurol* 2008;23:916–18.
- 7 Tohyama J, Akasaka N, Saito N, *et al*. Megalencephaly and polymicrogyria with polydactyly syndrome. *Pediatr Neurol* 2007;37:148–51.
- 8 Tore HG, McKinney AM, Nagar VA, *et al*. Syndrome of megalencephaly, polydactyly, and polymicrogyria lacking frank hydrocephalus, with associated MR imaging findings. *AJNR Am J Neuroradiol* 2009;30:1620–2.
- 9 Gripp KW, Hopkins E, Vinkler C, *et al*. Significant overlap and possible identity of macrocephaly capillary malformation and megalencephaly polymicrogyria-polydactyly hydrocephalus syndromes. *Am J Med Genet A* 2009;149A:868–76.
- 10 Verkerk AJ, Schot R, van Waterschoot L, *et al*. Unbalanced der(5)t(5;20) translocation associated with megalencephaly, perisylvian polymicrogyria, polydactyly and hydrocephalus. *Am J Med Genet A* 2010;152A:1488–97.
- 11 Riviere JB, Mirzaa GM, O'Roak BJ, *et al*. De novo germline and postzygotic mutations in AKT3, PIK3R2 and PIK3CA cause a spectrum of related megalencephaly syndromes. *Nat Genet* 2012;44:934–40.

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