Child's Nervous System
https://doi.org/10.1007/s00381-023-06150-5

CASE REPORT

Syndrome of megalencephaly, mega corpus callosum, and complete lack of motor development: an unusual case and a literature review

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Received: 1 August 2023 / Accepted: 5 September 2023

Abstract

The syndrome of megalencephaly, mega corpus callosum (MEG-MegaCC) accompanied by complete lack of motor development is a rare condition with only few sporadic cases having been reported in the literature. In this paper, we describe a child from non-consanguineous parents presenting with MegaCC, psychomotor retardation, and language impairment linked to MEG-MegaCC syndrome. Genetic analysis, radiological findings, and detailed neurological phenotype of MEG-MegaCC syndrome with its overlapping syndromes would allow for a better classification of the disease spectrum.

Keywords Mega corpus callosum · Megalencephaly · Macrocephaly · Psychomotor retardation · Developmental delay

Introduction

The corpus callosum is vital for communicating and integrating motor and somatosensory information between the cerebral hemispheres and for bilateral motor coordination and function [1]. Corpus callosum thickening in infancy and childhood has been associated with normal development, with the most significant thickening occurring at the splenium and midbody of the corpus callosum. An enlarged corpus callosum can present with Cohen syndrome and neurofibromatosis type 1, which are well-known syndromes [2, 3]. An increase in the number and size of the axons has been proposed as a possible explanation for the large size of the corpus callosum. Another possible mechanism is the reduction in the apoptotic process, resulting in reduced axonal elimination through the mediation of the protein neurofibromin. This thickness also reflects the volume of the cerebral hemispheres [1, 4].

The syndrome of megalencephaly, mega corpus callosum (MEG-MegaCC) accompanied by complete lack of motor development comprises progressive macrocephaly, marked psychomotor delay, mega corpus callosum, distinctive facies with frontal bossing, depressed nasal bridge, and long palpebral fissures. Since the first case was published by Göhlich-Ratmann et al. in 1998, 11 sporadic cases have been described [5–8]. In this paper, we report the 12th case of MEG-MegaCC syndrome and present clinical and magnetic resonance imaging (MRI) findings.

Case report

An 18-month-old boy presented to our clinic due to macrocephaly. He was the second child of healthy non-consanguineous parents, born via spontaneous vaginal delivery without any postnatal complications after a full-term pregnancy. There was no remarkable event in the prenatal and perinatal periods. There was also no family history of neurodevelopmental disorders.

Birth weight was 3350 gr (50 p), and birth head circumference was 35 cm (50 p). The child had a progressively

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Published online: 09 September 2023

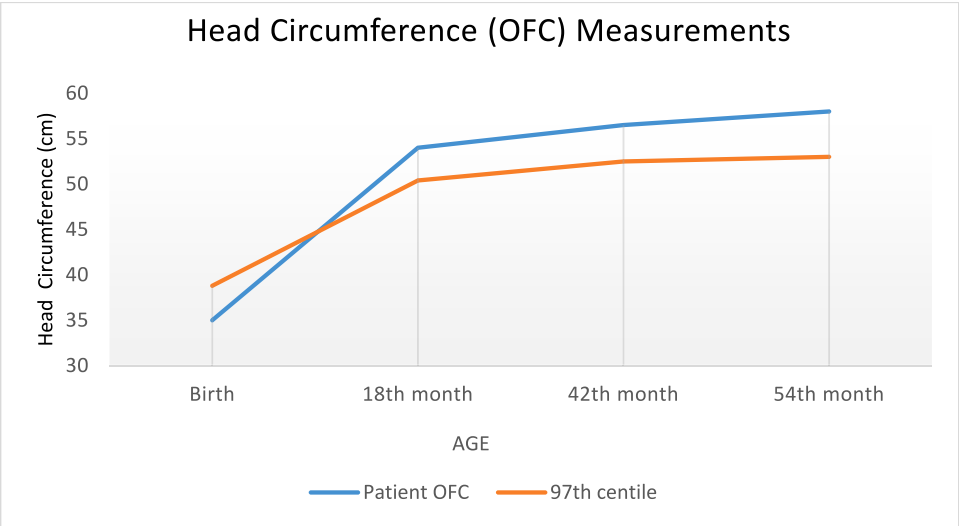

Fig. 1 Growth chart depicting serial head circumference measurements (0–54 months)

enlarging head that was first noticed when he was six months old. All the records of his head circumference measurements were greater than the 97th centile since he was 6 months (Fig. 1). His motor and mental development was markedly delayed, but his hearing, vision, and feeding were normal.

His face was very dysmorphic, with a broad forehead, frontal bossing, long palpebral fissures, a wide nasal bridge, low-set ears, a thin upper lip, and a wide philtrum. There was no neurocutaneous stigma (Fig. 2). Other physical and neurological examination findings were normal. Complete blood count, serum biochemistry, tandem mass, serum amino acids, and urine organic acids were also within normal limits. Therefore, basic metabolic diseases were excluded. Chromosomal analysis revealed a normal male karyotype (46, XY). The electroencephalogram, visual evoked potential and brainstem auditory evoked potential of the patient were normal, and he had no seizures.

Magnetic resonance imaging (MRI) of the brain taken at the age of 2 years and control brain MRI at the age of 4 years showed similar findings: generalized thickening of the cortex and megalencephaly. No sulcation abnormality or migration disorder was detected. All the components of the corpus callosum were significantly thickened, which was consistent with mega corpus callosum. Diffusely dilated Virchow-Robin spaces were detected in all white matter, bilateral basal ganglia, and the corpus callosum (Fig. 3). The ventricle sizes were considered within the normal range, and persistent cavum septum pellucidum et vergae was present. The magnetic resonance spectroscopy of the brain was normal.

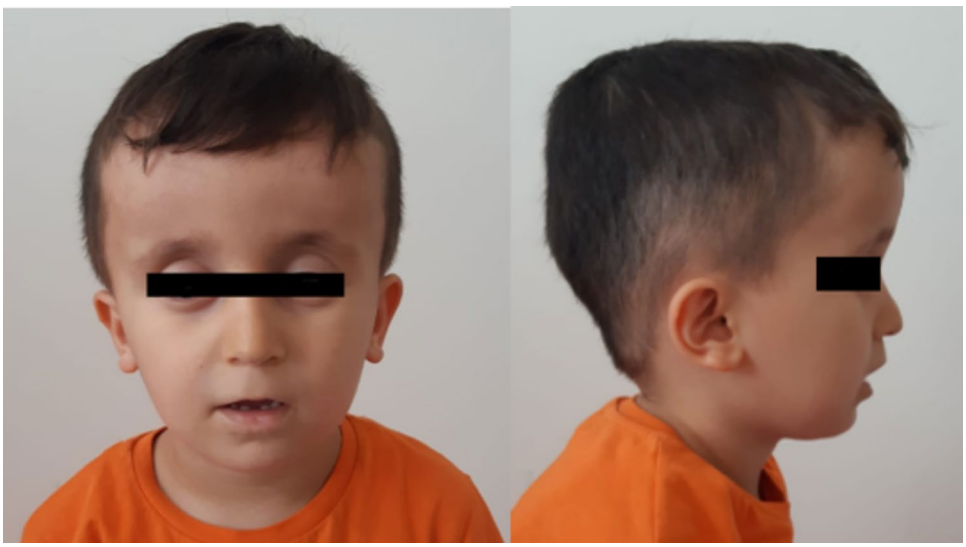

Fig. 2 Dysmorphic face findings: a broad forehead, frontal bossing, long palpebral fissures, a wide nasal bridge, low-set ears, a thin upper lip, and a wide philtrum

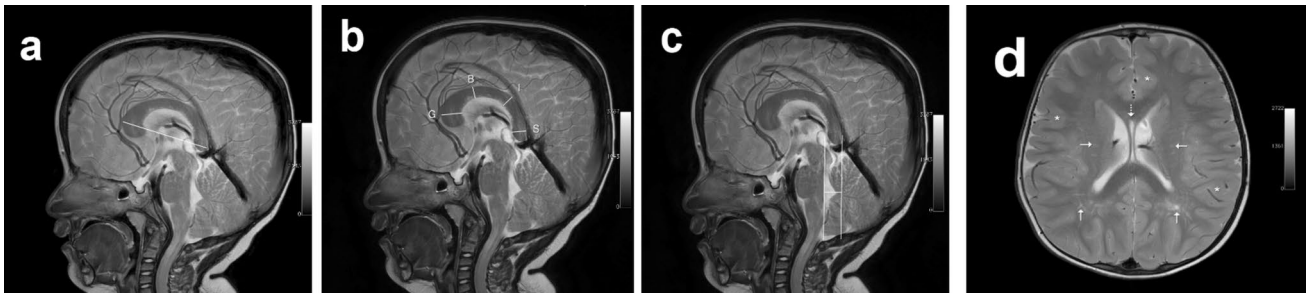

Fig. 3 T2-weighted brain magnetic resonance images in the sagittal and axial planes taken at the age of 4 years, showing different biometric parameters of mega-corpus callosum and other findings. **a** Measurement of the anteroposterior diameter of the corpus callosum (CC) (96 mm: above the 97th centile), the distance between the anterior aspect of the genu, and the posterior aspect of the splenium. **b** Measurement of the thickness of CC: at the level of the genu = 16 mm, body = 9 mm, isthmus = 6 mm, and splenium = 10 mm (all measurements were at or above the 97th centile). **c** Evaluation of the position of the splenium. A line was drawn along the dorsal surface of the brain stem. Another line was drawn parallel to the first one and passing at the level of the most posterior point of the splenium. The S/T distance between these lines was measured at the level of the fastigium. S/T (position of the splenium related to the tegmentum) = 12 mm (above the 97th centile). **d** Diffusely thickened cortex (stars) and diffuse dilated Virchow-Robin spaces (arrows), and the cavum septum pellucidum (dotted arrow)

The clinical and brain MRI phenotype was consistent with MEG-MegaCC syndrome accompanied by the complete lack of motor development. An early intervention developmental program was initiated.

Discussion

MEG-MegaCC syndrome is a rare condition, and our case is the 12th reported in the literature. Based on the initial description of MEG-MegaCC syndrome by Gohlich-Ratmann et al. in 1998, the clinical phenotype involves macrocrania, psychomotor retardation, and typical facies. The MRI phenotype indicates megalencephaly, thickening of gray matter with focal pachygyria, and mega corpus callosum [5]. However, when all reported cases are compared, it is seen that phenotypic features are no longer restricted to the original description. Contrary to the nomenclature, megalencephaly is not universally seen, and in the literature, it was reported to be absent in three children [9–11]. Polymicrogyria (PMG) can be one of the components of the MRI phenotype. MEG-MegaCC syndrome with PMG was referred to as MEG-PMG-MegaCC by Pierson et al. and Budai et al. [9, 10]. Table 1 presents the clinical and MRI phenotypes of all cases reported to date.

Currently, MEG-MegaCC syndrome is diagnosed based on the brain MRI phenotype and clinical features. However, the underlying etiology of these features remains unclear. Standard clinical, metabolic, and genetic testing has been of no support in linking the causation of this syndrome. It has been hypothesized that MEG-MegaCC syndrome and underlying cerebral overgrowth may result from the somatic mutations of a growth-regulating gene or occur spontaneously [7, 12].

The closest differential diagnosis of MEG-MegaCC syndrome is megalencephaly–polymicrogyria–postaxial polydactyly and hydrocephalus (MPPH) syndrome. Mirzaa et al. reported five cases with MPPH syndrome and suggested that their findings overlapped those of MEG-PMG-MegaCC syndrome [13]. The comparison of patients with MEG-MegaCC syndrome and MPPH syndrome revealed that both groups presented with megalencephaly, polymicrogyria, widened opercula, and severe retardation; however, none of the individuals with MPPH syndrome exhibited a thickened corpus callosum. In addition, polydactyly and hydrocephalus are not expected findings in patients with MEG-PMG-MegaCC syndrome [10].

Mutations in MAST1 gene variants result in mega corpus callosum syndrome with cortical malformations (MCC-CM) and mega corpus callosum syndrome with cerebellar hypoplasia and cortical malformations (MCC-CH-CM). Therefore, this entity has different names according to the presence or absence of cerebellar hypoplasia [14, 15]. Our patient's MRI and clinical phenotype did not support the diagnosis of MCC-CM syndrome. Therefore, mutations in the MAST1 gene were not specifically analyzed. According to literature, craniosynostosis can also cause thicker corpus callosum but differs from other diseases by having microcephaly [16].

Our patient was diagnosed with a typical phenotype and pathognomonic MRI features of MEG-MegaCC syndrome. A comprehensive genetic analysis and detailed neurological phenotype of MEG-MegaCC syndrome with its overlapping syndromes would allow for a better classification of the disease spectrum.

Table 1 Comparison of the clinical findings and brain MRI phenotype of the MEG-MegaCC syndrome cases reported in the literature

References	Göhlich-Ratmann et al. [5]			Dagli et al. [7]	Pierson et al. [10]	Bindu et al. [11]		Hengst et al. [8]	Agarwal et al. [4]	Budai et al. [9]	Park et al. [6]	Current study
	Case 1	Case 2	Case 3	Single case	Single case	Case 1	Case 2	Single case	Single case	Single case	Single case	Single case
Age	5.5 years	2 years	4 years	15 months	9 years	5 years	10 years	3 years	3.5 years	4 years	2 years	4 years
Sex	Male	Female	Female	Female	Male	Female	Male	Female	Male	Female	Male	Male
Megalencephaly	Present	Present	Present	Present	Absent	Absent/microcephaly present	Absent/microcephaly present	Present	Present	Absent	Present	Present
Ventricles	Slight dilation	Slight dilation	Slight dilation	Normal	Dilated lateral ventricles	Moderate dilatation of the fourth ventricle	Moderate dilatation of the fourth ventricle	Slight dilation	Normal	Normal	Normal	Normal
Corpus callosum	Thick	Thick	Thick	Thick	Thick	Thick	Thick	Thick	Thick	Thick	Thick	Thick
Diffusely dilated Virchow-Robin spaces	Absent	Absent	Absent	Present	Absent	Present	Present	Absent	Absent	Absent	Absent	Present
Other neuroimaging findings	Enlarged white matter, focal pachygyria, and wide sylvian fissures	Enlarged white matter, focal pachygyria, wide sylvian fissures, and left periventricular heterotopia	Enlarged white matter, focal pachygyria, and wide sylvian fissures	Generalized cortical thickening and normal Sylvian fissures normal	Sylvian fissures with incomplete opercularization, bilateral polymicrogyria, and dysplasia of the putamen and globus pallidus	Diffusely thickened cortex, polymicrogyria Sylvian fissures with incomplete opercularization, pontine hypoplasia, hypoplastic cerebellar vermis, and abnormal foliation	Diffusely thickened cortex, polymicrogyria, Sylvian fissures with incomplete opercularization, pontine hypoplasia, hypoplastic cerebellar vermis, and abnormal foliation	Generalized polymicrogyria causing pachygyric appearance and sparing of cortical structures adjacent to the midline and visual cortex	Enlarged white matter, pachygyria, wide Sylvian fissures, persistent cavum septum pellucidum, and medial rotation of the hippocampi	Sylvian fissures with incomplete opercularization, bilateral polymicrogyria	Generalized cortical thickening and normal Sylvian fissures	Generalized cortical thickening, normal Sylvian fissures, persistent cavum septum pellucidum, and diffusely dilated Virchow-Robin spaces in all white matter

Table 1 (continued)

References												
	Göhlich-Ratmann et al. [5]			Dagli et al. [7]	Pierson et al. [10]	Bindu et al. [11]		Hengst et al. [8]	Agarwal et al. [4]	Budai et al. [9]	Park et al. [6]	Current study
	Case 1	Case 2	Case 3	Single case	Single case	Case 1	Case 2	Single case	Single case	Single case	Single case	Single case
MR spectroscopy findings	No data	Normal	No data	No data	Slight lactate elevation	No data	No data	Normal	No data	No data	No data	Normal
Fine motor skills/tone	Psychomotor retardation, hypotonia, muscle atrophy, knee contractures, scoliosis, rigor, and no head control	Psychomotor retardation, hypotonia, brisk reflexes, and no head control	Psychomotor retardation, hypotonia, and no head control	Psychomotor retardation and hypotonia	Psychomotor retardation, hypotonia, and wheelchair-bound	Psychomotor retardation, dystonic posturing, walking with a stoop, and frequent falls	Psychomotor retardation, dystonic posturing, and awkward and clumsy gait/mildly increased tone	Psychomotor retardation, hypotonic, poor head control, clonic, and moving by rolling sidewards	Psychomotor retardation and no head control/hypotonia	Psychomotor retardation, axial hypotonia, and dysphagia, especially for liquids	Isolated hypertonicity of the right lower extremity	Psychomotor retardation
Speech	No vocalization	No vocalization	No vocalization	No vocalization	Non-verbal, did not follow commands	No vocalization could not understand simple commands	A vocabulary of a few words	No vocalization	Vocalization only	No vocalization	One-word sentences	A vocabulary of a few words
Epilepsy	Absent	Absent	Present (not specified)	Infantile spasms and West syndrome	Partial epilepsy (simple-complex)	Generalized tonic–clonic/myoclonic jerks	Refractory myoclonic	Absent	Generalized tonic-clonic	No data	Absent	Absent
Facial dysmorphia	Broad forehead and large eyes	Frontal bossing and low nasal bridge	Broad forehead and large eyes	Tent-shaped mouth, frontal bossing, open anterior fontanel, ptosis, and long palpebral fissures	Frontal bossing and low nasal bridge	Depressed nasal bridge	Absent	Absent (submucous cleft palate)	Broad forehead, long palpebral fissures, wide nasal bridge, small columella, and wide philtrum	No data	No data	Broad forehead, frontal bossing, long palpebral fissures, wide nasal bridge, low ears, thin upper lip, and wide philtrum

Table 1 (continued)

References	Göhlich-Ratmann et al. [5]			Dagli et al. [7]	Pierson et al. [10]	Bindu et al. [11]		Hengst et al. [8]	Agarwal et al. [4]	Budai et al. [9]	Park et al. [6]	Current study
	Case 1	Case 2	Case 3	Single case	Single case	Case 1	Case 2	Single case	Single case	Single case	Single case	Single case
Maternal pregnancy history	Uneventful	Uneventful	Uneventful	Uneventful	One abortion	Uneventful	Uneventful	Two abortions	Uneventful	Normal pregnancy was normal until the eighth month, had an abdominal trauma involving loss of consciousness	No data	One abortion

MEG-MegaCC megalencephaly and mega-corpus callosum, *MR* magnetic resonance

Declarations

Conflict of interest None.

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