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Clinical Observations

White Matter Lesions Detected by Magnetic Resonance Imaging in Neonates and Children With Congenital Myotonic Dystrophy

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ABSTRACT

Background: Congenital myotonic dystrophy (CDM1) is an autosomal dominant genetic disorder caused by abnormal cytosine-thymine-guanine trinucleotide repeat expansion that results in weakness and cognitive deficits. Studies detailing brain magnetic resonance imaging (MRI) findings in neonates and children with this condition are limited.
Objective: We evaluated the brain MRI findings in children, including neonates with CDM1, to assess the nature of central nervous system involvement and progression of MRI lesions over time.
Methods: The Cincinnati Children's Hospital neuromuscular disease database was used to identify 16 patients with CDM1 with genetically proven CDM1 who had undergone brain MRI. Hospital charts were reviewed to collect clinical information.
Results: Ninety-four percent of patients had an abnormal MRI showing injury to the white matter. Nine patients underwent imaging before eight days of life, and eight of these patients showed signs of injury to the white matter. Three neonates had follow-up MRI scans, and all showed progression of injury. Seven patients had the first MRI between age 29 days and 22 years, and all had abnormalities involving the white matter. Two patients had additional congenital brain malformations, and one patient also harbored a mutation in CDKL5 with resultant epilepsy.
Conclusions: White matter abnormalities are found in patients with CDM1, even in the neonatal period. Many patients present with hypoxia and receive a diagnosis of hypoxic-ischemic encephalopathy and may even undergo therapeutic hypothermia. If MRI findings of white matter injury do not correlate with hypotonia and weakness, further evaluation for CDM1 should be considered.

Introduction

Congenital myotonic dystrophy (CDM1) is an autosomal dominant, multisystem disorder that presents soon after birth with hypotonia and weakness. The gene associated with CDM1 is dystrophia myotonica protein kinase (DMPK), and symptomatic disease is associated with a cytosine-thymine-guanine trinucleotide repeat expansion on the 3′ untranslated region of the DMPK gene located on chromosome 19q13.3.[1]

Most magnetic resonance imaging (MRI) studies to date of CDM1 have primarily evaluated older children and adults with this condition.[2-10] There are a limited number of studies detailing MRI findings in children, particularly neonates, with CDM1. There are case reports describing neonatal imaging findings in patients with CDM1, which include nonspecific white matter abnormalities, enlarged ventricles, and a simplified gyral pattern.[11,12] Studies evaluating MRI in older children and adults show findings of cortical atrophy, thin corpus callosum, ventriculomegaly, and periventricular hyperintensities.[2-10] The goal of our study was to evaluate brain MRI findings in a larger cohort of children, including

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10 neonates with CDM1, to assess the nature of central nervous system (CNS) involvement and investigate the progression of MRI lesions over time. Finally, with advancements in prenatal MRI, we wanted to determine whether the lesions could be detected in fetal images.

Methods

Study design

After obtaining institutional review board approval (IRB #2017-2891) for a retrospective study, we queried the Cincinnati Children's Hospital neuromuscular disease database for patients with CDM1 who were treated between January 2000 and May 2017 and identified 18 subjects. Study inclusion criteria required a genetically proven CDM1 diagnosis as well as a brain MRI. Two subjects were excluded secondary to only MRI reports being available. Fetal imaging was available for two patients. Hospital charts were reviewed to collect clinical information.

Image interpretation

All fetal and postnatal MRIs were reviewed by a neuroradiologist (U.D.N.), who was unaware of prior imaging reports and clinical outcomes. When present, diffusion-weighted images (DWIs) with their corresponding apparent diffusion coefficient maps were reviewed for the presence or absence of true diffusion restriction in the brain parenchyma, presumed to represent acute or subacute infarct. The presence or absence as well as the number of abnormal T2/fluid-attenuated inversion recovery hyperintense white matter signal abnormalities or T1 hyperintense signal abnormalities, presumed to represent areas of injury, were also recorded. White matter volume loss was subjectively assessed as mild, moderate, or severe. The presence or absence of congenital brain malformation and its description was also assessed.

Review of other studies

We reviewed previous MRI studies of patients with CDM1 (Table 1). We only included publications wherein a congenital onset was identified and MRI findings clearly pertained to patients with CDM1; thus studies wherein MRI findings of patients with congenital and adult-onset myotonic dystrophy were grouped together, without distinguishing findings between the two groups, were excluded.

Results

Demographics and outcomes

We examined 16 patients with a diagnosis of CDM1 who underwent MRI scans. There were nine males and seven females (Table 2). Ten subjects were born at term, whereas four were born prematurely (mean 32.5 weeks) (Supplemental Table 1). Gestational age was unknown for two patients. Four of 16 patients are deceased. The current age of the remaining 12 patients ranges from two to 23 years (Supplemental Table 1).

Detailed perinatal data were available for 12 patients. One-minute Apgar score ranged from 1 to 7 (Supplemental Table 1). Five patients were diagnosed with hypoxic-ischemic encephalopathy (HIE) based on clinical presentation, and one subject underwent therapeutic hypothermia. All patients with available detailed perinatal information (n = 12) required respiratory support at birth

TABLE 1.
Previous Brain MRI Studies of Myotonic Dystrophy Patients

Author	Year	Mean CTG Repeat (S.D.)	Total # Patients	# CDM	Age at MRI Scan	MRI Abnormalities
Tanabe[3]	1992	NR	7	7	2-8 years	Periventricular hyperintensities, ventriculomegaly
Hashimoto[5]	1995	NR	13	7	NR	Dilatation of lateral or third ventricle, increased signal in centrum semiovale or periventricular region, small corpus callosum in four patients and cortical atrophy in three patients
Bachmann[7]	1996	NR	40	5	Average age 36 years	Cerebral atrophy in 68%, WM lesions in 65%, temporal lobe lesions in 23%, wide Virchow-Robin spaces in 38%
Chang[6]	1998	846.8 (313.8)	14	1	2.5 years	Mild generalized atrophy in patient with CDM
Martinello[4]	1999	1847 (411)	5	5	5 - 19 years	Dilatation of lateral or third ventricle, cortical atrophy, hypoplasia of corpus callosum
Di Constanzo[8]	2002	572.2 (359)	25	5	13-32 years (13, 18, rest >18)	CDM had increased WM hyperintensities and ventricle:brain ratio than age-matched adult DM1 or normal controls but similar to disease-duration-matched adults, WM lesions frequently limited to areas posterior and inferior to trigones
Kuo[10]	2005	525 (418)	6	2	13-15 years	CDM had hyperintensity of WM posterior and superior to trigone, thinned corpus callosum, ventriculomegaly
Franc[9]	2012	554.5 (NR)	10	5	24-34 years	WM pathology throughout cerebrum, DTI/FA showed more abnormalities than FLAIR; adult DM1 with lower measures of WM integrity than CDM; CDM and DM1 with significantly lower FA than controls in inferior frontal, supracallosal, and occipital regions; significantly lower gray matter volumes in all DM groups when compared WITH controls
Bosemani[11]	2014	943	1	1	46 days (corrected 36 gestational weeks) follow-up: 4 months of life	Initial MRI: Diffuse T2 hyperintensity of supratentorial white matter, mild ventricular dilatation, simplified gyral sulcal pattern Follow-up MRI: Relative decrease and normalization of the T2-weighted WM signal, mild ventricular dilatation and prominence of interhemispheric spaces, more complex gyral sulcal pattern

Abbreviations:
CDM = Congenital myotonic dystrophy
DM1 = myotonic dystrophy type 1
DTI = Diffusion tensor imaging
FA = Fractional anisotropy
FLAIR = Fluid attenuated inversion recovery
MRI = Magnetic resonance imaging
NR = Not reported
WM = White matter

TABLE 2.
MRI Findings in CDM1 Patients

Patient	Gender	CTG Repeats	Age at Initial MRI Scan	Age at Repeat MRI Scans	Number of Focal White Matter Lesions	Location of Lesions	White Matter Volume Loss	Description of MRI Abnormalities
1	Male	CTG expansion reported without number of CTG repeats	11 years	16 years 18 years	4	1, 2, 4	11 years: 0 16 years: 0 18 years: 0	Hypomyelination, T2/FLAIR WM signal abnormalities, normal MRA
2	Male	1300	1 day	N/A	1	2	0	T1 bright foci of right periatrial WM injury, mildly enlarged extra-axial CSF spaces suggest mildly decreased cerebral volume, normal MRS
3	Female	2400	4 years	N/A	0	N/A	3	Severe supratentorial WM volume loss
4	Male	2100	4 days	N/A	0	N/A	1	Mild enlargement of the lateral ventricles, likely reflecting some degree of decreased brain parenchymal volume; delayed myelination; simplified gyral pattern
5	Male	1370	3 years	N/A	No	N/A	2	Moderate supratentorial WM volume loss, gliosis
6	Male	1800	22 years	N/A	4	1, 2, 3, 4	2	Moderate supratentorial WM volume loss, multifocal T2/FLAIR white matter signal abnormalities, normal MRA and MRS
7	Male	1600	6 days	7 weeks	4	1, 2, 4	6 days: 1 7 weeks: 3	6 days: Acute/subacute WM injury, PLIC diffusion restriction 7 weeks: WM volume loss significantly progressed
8	Male	1400	7 months	7 years	4	2, 4	7 months: 1 7 years: 1	7 months: Increased T2 signal in bilateral globi pallidi, enlarged subarachnoid space over right cerebral hemisphere 7 years: Foci of posterior periventricular white matter gliosis bilaterally
9	Female	1600	6 days	N/A	0	N/A	0	Normal MRI
10	Female	1250	5 days	N/A	3	1, 2, 4	0	Foci of T1 hyperintense WM injury, one focus with subtle diffusion restriction, normal MRS
11	Female	1500	8 days	N/A	0	N/A	2	Mild or moderate enlargement of the lateral ventricles, most pronounced at the occipital and temporal horns, thinning of the corpus callosum, mild cerebellar and vermian hypoplasia, borderline myelination
12	Female	1600	7 days	16 months 3 years	0	N/A	7 days: 2 16 months:3 3 years: 2	7 days: Right germinal matrix haemorrhage 16 months: Hypomyelination, no focal signal abnormalities 3 years: Status post shunt, diffuse periventricular T2/FLAIR hyperintensity, MMC, Chiari II
13	Male	2300	2 years 4 years	N/A	0	N/A	2 years: 2 4 years: 2	Mild to moderate ventriculomegaly, primarily involving the occipital horns of the lateral ventricles
14	Female	2100	29 days	N/A	0	N/A	1	Mild diffuse increased T2 signal throughout the WM, questionable abnormal hyperintense T1 and T2 signals in the globus pallidus bilaterally, ventricles are upper normal in size for age, as are the subarachnoid fluid spaces
15	Female	1700	7 days	3 months 20 months	4 (7 days), 2 (3 months), 4 (20 months)	1,2,3,4	7 days: 0 3 months: 1 20 months: 2	7 days: Enlarged subarachnoid fluid spaces, scattered foci of small areas of diffusion restriction in bilateral periventricular white matter 3 months: Gray matter heterotopia more clearly seen, enlarged subarachnoid spaces 20 months: Further progression of WM volume loss
16	Male	1173	5 days	N/A	0	N/A	3	Lateral and third ventriculomegaly, small area of restricted diffusion related to atria of lateral ventricles

Abbreviations:
CSF = Cerebrospinal fluid
CTG = Cytosine-thymine-guanine
CDM = congenital myotonic dystrophy
DM1= myotonic dystrophy type 1
FLAIR = Fluid-attenuated inversion recovery
MRA = Magnetic resonance angiography
MRI = Magnetic resonance imaging
MRS = Magnetic resonance spectroscopy
MMC = Myelomeningocele
N/A = Not applicable
PLIC = Posterior limb of internal capsule
WM = White matter
White matter volume loss: 0 = normal, 1 = mild, 2 = moderate, 3 = severe
Quantification of white matter lesions: 4 or greater is denoted as 4
Location of lesions: 1 = frontal, 2 = parietal, 3 = occipital, 4 = temporal

(Supplemental Table 1). In long term, of the surviving patients, one patient has required no support and respiratory support is unknown for one patient. The remaining 10 patients require chronic respiratory support (Supplemental Table 1). With regard to feeding support, five patients require ongoing assistance via nasogastric or gastrostomy tube (Supplemental Table 1). In the neonatal period, all patients had hypotonia, two patients had micrognathia, one had facial diplegia, and one had paralysis of the right hemidiaphragm (Supplemental Table 1).

Imaging

Initial MRI scans were performed between age two days and 22 years. Infants admitted to the neonatal intensive care unit for hypotonia and weakness requiring intubation routinely undergo MRI studies to evaluate for a central cause. Furthermore, five infants were diagnosed with HIE at birth; these infants routinely undergo MRI for the purpose of prognostication. Of the 16 subjects, one patient had a normal MRI on the sixth day of birth; this patient is currently aged 11 years and has not undergone a repeat MRI (Table 2).

Initial MRI done within first eight days of life

The initial MRI was obtained within the first eight days of life in nine patients. A DWI sequence was not obtained in one patient. Four of eight patients (50%) had small foci of abnormal diffusion restriction within the subcortical and periventricular white matter, suggestive of ischemic injury. Four patients had no DWI changes but had thinning of the corpus callosum and abnormal T1 and T2 signal in the white matter (Table 2).

Three patients had repeat MRI scans, and all showed progression of white matter injury. Specifically, two patients had progressive thinning of the white matter. One patient (#15) had progressive thinning of the white matter and transient decrease in the number of lesions on MRI performed at three months of life, but then had an increase in white matter lesions at 20 months of life, suggesting progressive injury.

Two patients with neonatal MRIs were noted to have congenital brain malformation. One had a Chiari II malformation and meningomyelocele that was detected on fetal MRI performed at 28 weeks gestational age. Another patient was noted to have gray matter heterotopias on a follow-up scan performed at age three months. Interestingly, this patient was subsequently found to harbor a likely pathogenic mutation in CDKL5 and has epilepsy in addition to CDM1. Another patient with DWI changes noted on postnatal imaging and initially diagnosed with HIE was noted to have bilateral ventriculomegaly on fetal MRI performed at 36 weeks three days gestational age.

Initial MRI done after 29 days of life

Seven patients were older at the time of the first MRI (29 days to 22 years of age). None of these patients had a normal MRI, and all had evidence of white matter injury (Table 2; Fig). Three had multiple MRI scans, and only one patient who was first imaged at age six months showed progression of lesions. Patient #8 was noted to have mild white matter thinning at age six months; imaging done at age seven years showed development of numerous white matter lesions. Overall, our findings are consistent with previously reported studies (Tables 1 and 2) and note findings of ventriculomegaly and white matter hyperintensities. There is great variability among patients with regard to the number and location of lesions (Tables 1 and 2), which does not correspond to cytosine-thymine-guanine trinucleotide repeats; however, subcortical white matter in the parietal and temporal regions was most often involved in our study.

Discussion

CDM1 is an autosomal dominant, trinucleotide repeat disorder affecting the DMPK gene on chromosome 19q13.3[1] that often presents in the neonatal period with hypotonia, weakness, and encephalopathy. There is paucity of research detailing MRI findings in neonates and young children with CDM1. Our cohort of 16 subjects is the largest reported study to date of MRI features in 10 neonates and five children younger than 11 years with CDM1. In our study, 94% of patients (15 of 16) had an abnormal MRI.

In neonates who underwent imaging within the first eight days of life, all but one neonate had imaging findings of mild white matter injury. Importantly, evaluation of the clinical course of babies who were initially diagnosed with HIE did not correlate with imaging findings. Specifically, they had notable hypotonia and required significant respiratory and feeding support; MRI did not show injury to deep brain structures as would be expected if symptoms were to be attributed to severe HIE. Our findings emphasize that caution must be exercised to not erroneously make a diagnosis of HIE and attribute perinatal encephalopathy and weakness to mild white matter injury seen on MRI.

Two patients underwent fetal imaging. One patient was noted to have ventriculomegaly. Ventriculomegaly is a common finding on prenatal ultrasound leading to referral for further evaluation with MRI. Combination of ventriculomegaly with postnatal clinical examination findings of hypotonia and weakness should raise suspicion for CDM1. In addition, assessment of maternal grip prenatally in cases of coexisting polyhydramnios and talipes is an important diagnostic aid for CDM1. Observation of ventriculomegaly prenatally,[13] and neonatally,[15] using ultrasound have been noted previously. It is possible that CNS involvement in this condition is the direct consequence of the genetic disorder. Ventricular dilation in CDM1 was found to be loosely correlated with cognitive deficits in a cohort of five patients.[4] For patients with adult-onset myotonic dystrophy type 1, no difference in cognitive function has been noted between patients with mild ventricular versus severe dilation.[14]

Six patients underwent multiple MRI scans, and 50% (three of six) demonstrated progression of white matter lesions. Although there is no literature detailing how the abnormal gene product specifically affects the CNS, our data raise the possibility of a predisposition to white matter injury and ongoing white matter injury secondary to this product. Although we know that white matter signal abnormalities are very nonspecific, in this patient population we can assume they represent gliotic changes for a number of reasons. First, these signal abnormalities are associated with white matter volume loss. Moreover, these signal abnormalities persist on subsequent examinations and do not appear to resolve, making acute or subacute reversible processes less likely. Finally, white matter injury would be consistent with the presumed neurodegenerative nature of the disease. Studies evaluating MRI in older individuals with myotonic dystrophy find correlation between MRI findings and functional deficits.[7]

Timing of progression of white matter lesions is unclear. Interestingly, two patients with MRI done after age two years had no progression of lesions when imaging was repeated. However, two patients imaged before age six months showed an increase in

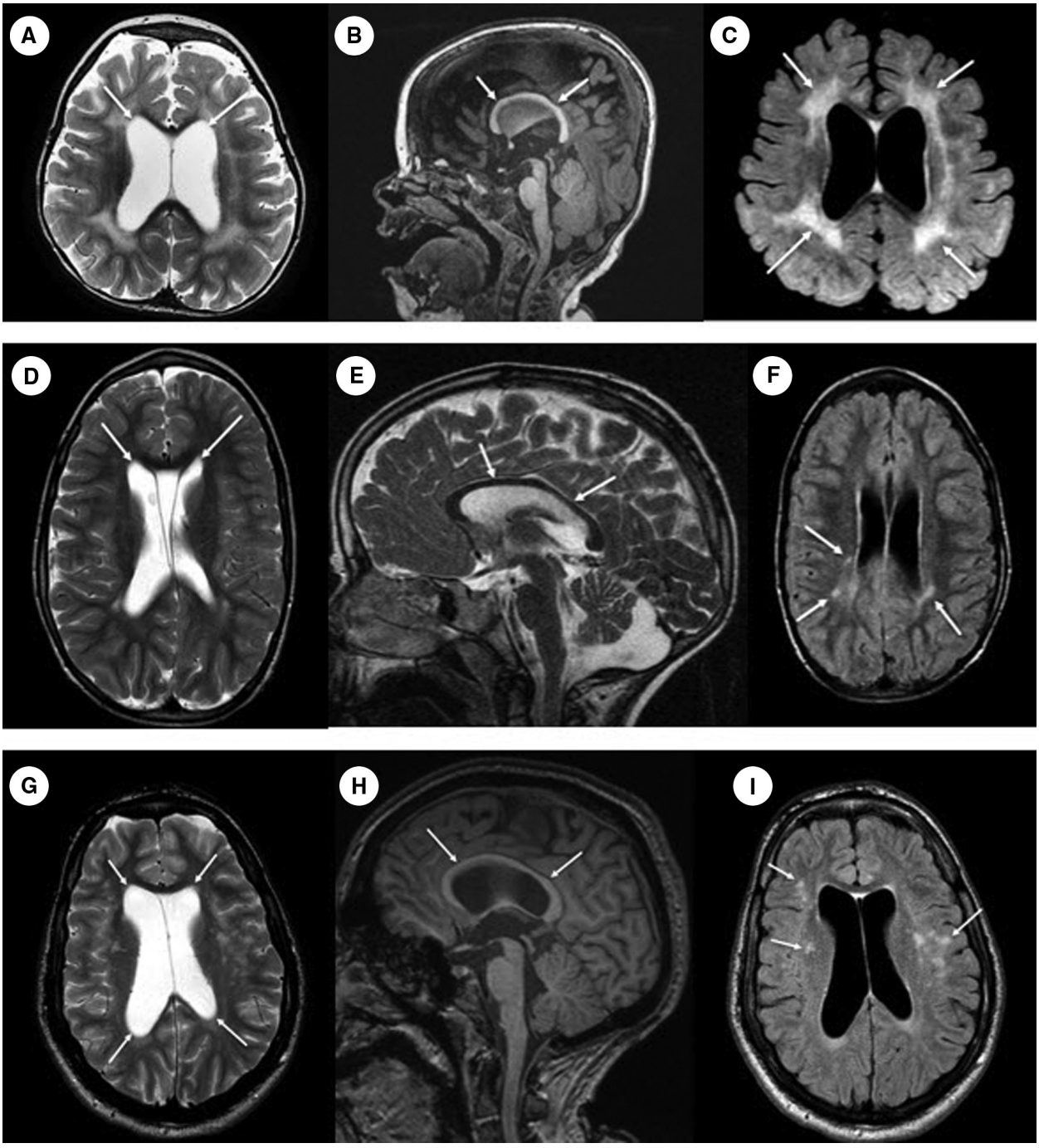

FIGURE. Brain magnetic resonance images from three different patients with congenital myotonic dystrophy. The first patient (A–C) is a 20-month-old female with decreased white matter volume marked by moderate ventriculomegaly of the lateral ventricles on T2 (A, *arrows*) and associated thinning of the corpus callosum seen on sagittal T1 (B, *arrows*). There is asymmetric confluent T2/ fluid-attenuated inversion recovery (FLAIR) hyperintense signal in the periventricular white matter (C, *arrows*). The second patient (D–F) is a seven-year-old male with milder intracranial findings with mild ventriculomegaly of the lateral ventricles on T2 (D, *arrows*) and associated thinning of the corpus callosum on sagittal T2 (E, *arrows*). There are a few foci of T2/FLAIR hyperintense periventricular white matter signal (F, *arrows*). The third patient (G–I) is a 22-year-old male also with mild ventriculomegaly of the lateral ventricles on T2 (G, *arrows*) with associated thinning of the corpus callosum on sagittal T1 (H, *arrows*). There are several T2/FLAIR hyperintense foci on FLAIR (I, *arrows*) in the left greater than right deep and subcortical white matter.

the number of lesions when imaged at an older age. A limitation of this study is that some of our patients underwent brain MRIs before age one year, during which myelination is not complete by imaging, decreasing the sensitivity of identifying small or subtle white matter signal abnormalities on these examinations. Thus although subsequent imaging examinations may appear progressed, we may not be able to appreciate the true extent of disease progression. Of note, the one patient with a normal MRI at six days of age has not undergone additional neuroimaging; it is possible that lesions may have emerged in this individual at a later age. Further longitudinal studies are needed to elucidate intracranial involvement with CDM1, its relationship to clinical symptoms, and the role of the abnormal gene product in contributing to disease progression.

Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2019.03.004.

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