The Shrunken, Bright Cerebellum: A Characteristic MRI Finding in Congenital Disorders of Glycosylation Type 1a

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The clinical presentation and course are highly variable, ranging in the gene encoding oligosaccharides. CDG-1a (OMIM#212065), caused by mutation in the gene encoding PMM2, is the most common form. The clinical presentation and course are highly variable, ranging from severe infantile multisystem involvement to mild late-onset forms. Muscular hypotonia, strabismus, and developmental delay are variably associated with dysmorphic features, abnormal subcutaneous fat distribution ("fat pads"), nipple retraction, feeding problems, and failure to thrive. Stroke-like episodes have also been reported. Brain MR imaging studies have consistently shown a small cerebellum, variably designated as cerebellar hypoplasia, olivopontocerebellar hypoplasia, or cerebellar atrophy. The purpose of this study is to describe the MR imaging findings on initial and follow-up studies in patients with CDG-1a and to identify suggestive MR imaging features that may prompt further diagnostic tests.

Materials and Methods
Institutional review board approval was not sought, as it is not required in our country for retrospective studies that do not involve patient identity disclosure. Five Italian children (3 males and 2 females, aged 12 days to 2 years at clinical presentation) with confirmed CDG-1a constitute the focus of this article. These patients were selected on the basis of a molecular genetic confirmation of the diagnosis and the availability of at least 1 MR imaging study for evaluation. We retrospectively reviewed their clinical, laboratory, electrophysiologic, and neurologic information. Laboratory investigations included routine blood work, analysis of transferrin by serum isoelectric focusing, and enzymatic analysis of PMM activity on skin fibroblasts.

ABBREVIATIONS: BAEP = brain stem auditory evoked potential; CA = cerebellar atrophy; CDG = congenital disorders of glycosylation; CH = cerebellar hypoplasia; EEG = electroencephalogram; ERG = electroretinogram; mIns = myo-inositol; NCV = nerve conduction velocity; PMM = phosphomannomutase; PRESS = point-resolved spectroscopy sequence; sI = scyllo-inositol; VEP = visual-evoked potentials

CDGs are genetically heterogeneous autosomal recessive disorders caused by abnormal glycosylation of N-linked oligosaccharides. CDG-1a (OMIM#212065), caused by mutation in the gene encoding PMM2, is the most common form.

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Table: MRI findings in 5 patients with CDG-1a

<table>
<thead>
<tr>
<th>Patients</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Age at first MRI</td>
<td>12 days</td>
<td>5 months</td>
<td>2 years</td>
<td>7 months</td>
<td>9 months</td>
</tr>
<tr>
<td>Age at second MRI</td>
<td>11 months</td>
<td>NA</td>
<td>16 years</td>
<td>2 years</td>
<td>3 years</td>
</tr>
<tr>
<td>Cerebellar volume loss at presentation</td>
<td>Mild</td>
<td>Severe</td>
<td>Severe</td>
<td>Moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Progressive cerebellar atrophy on follow-up</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cerebellar T2/FLAIR hyperintensity</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Supratentorial involvement</td>
<td>Delayed WM myelination, ventriculomegaly</td>
<td>No</td>
<td>Cortical atrophy, WM atrophy and gliosis, ventriculomegaly</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>DWI findings, cerebellum (s/mm²)</td>
<td>↑ ADC 1.589 (first MRI) 1.885 (second MRI)</td>
<td>↑ ADC 1.238</td>
<td>NA</td>
<td>NA</td>
<td>↑ ADC 1.032 (second MRI)</td>
</tr>
<tr>
<td>¹H-MRS findings (cerebellum)</td>
<td>NA</td>
<td>Quality insufficient</td>
<td>↑ mI/Cr ↑ sl/Cr ↓ Cho/Cr ↓ NAA/Cr ↑ αGlx</td>
<td>↑ mI/Cr ↓ Cho/Cr</td>
<td></td>
</tr>
</tbody>
</table>

Note: αGlx: alpha-glutamine/glutamate complex; NA, not available.

Results

Clinical, Neurophysiologic, Laboratory, and Molecular Findings

All children were born at term from healthy, unrelated parents after uncomplicated pregnancies and deliveries. Three subjects presented with muscular hypotonia, feeding difficulties, and failure to thrive, either in the neonatal period (cases 1 and 2) or in the second month of life (case 3). Case 4 presented with renal and hepatic involvement at 3 months, and case 5 with developmental delay at 7 months. Facial dysmorphism, inverted nipples, and fat pads were observed in 4 patients, hepatomegaly in 2 (cases 3 and 4), and renal cortical hyperchogenicity in 3 (cases 2–4). Neurologic examination showed strabismus, muscular hypotonia, and weakness in all children, with poor tendon reflexes related to peripheral neuropathy in 4. Laboratory investigations showed elevated transaminases in all patients as well as a type I transferrin isoform pattern at isoelectric focusing of serum transferrin. The diagnosis of infantile type CDG-1a was confirmed by significantly decreased PMM activity in fibroblasts and by the presence of PMM2 mutations in all patients. Neurophysiologic study showed slowing of motor NCV in 4 patients (cases 1, 3, 4, and 5), and normal NCV in the remaining patient at 15 months of life; reduced amplitude of VEP/ERG was found in 2 subjects (cases 2 and 3), and normal VEP/ERGs were found in 2 (cases 4 and 5); sensorineural abnormality at BAEP was found in 1 (case 3), whereas BAEPs were normal in the remaining 2 (cases 4 and 5). EEGs showed slow background activity in 2 patients (cases 1 and 3) and was normal in the other 2 (cases 2 and 5).

MR Imaging Findings

MR imaging findings are summarized in the Table. A variably severe reduction in size of the cerebellar folia, involving both the vermis and the hemispheres, with corresponding enlargement of the fissures was present in all patients (Fig 1). In 1 of them (case 1), MR imaging during the neonatal period showed inferior vermis hypoplasia, progressing to diffuse cerebellar volume loss on follow-up (Fig 2). In all patients in whom follow-up studies were available for review (cases 1, 3, 4, 5), the MR imaging examinations showed worsening, with progressive cerebellar volume loss (Fig 3). Careful analysis of vermis morphology showed that the volume of the superior vermis appeared to reduce uniformly, with a corresponding degree of folial diminution and fissural enlargement. In 4 cases (cases 1–4), the inferior vermis had a flat appearance both at presentation and on
follow-up, with a more rudimentary appearance of the individual folia and not particularly enlarged fissures (Figs 1 and 2). Only in 1 case (case 5), in which the degree of cerebellar volume loss was very mild, the cerebellar vermis had a near-normal appearance with only mild folial volume reduction at presentation, which progressed on follow-up.

A second characteristic feature consisted of cerebellar cortical hyperintensity on long TR (ie, T2-weighted and FLAIR) images (Fig 1), observed at presentation in 3 cases (cases 2, 3, 4) and on follow-up in the other 2. The subcortical white matter also appeared mildly hyperintense, especially in the FLAIR images, resulting in a globally hyperintense appearance of the cerebellum in 4 patients (cases 1–4) (Figs 1–3). The middle cerebellar peduncles had normal signal intensity in all cases. The dentate nuclei were hyperintense in 1 patient (case 5). DWI consistently showed increased diffusion within the cerebellum, involving both the cortex and subcortical white matter.

The brain stem appeared abnormal in 4 patients (cases 1–4). The abnormality consisted of a reduced bulge of the pontine protuberance (Figs 1–3) that was progressive on follow-up studies in 3 cases, paralleling cerebellar volume loss (Figs 2 and 3). There was a pontine “hot cross bun” sign in 1 case (case 3), consisting of T2-hyperintense transverse fibers and median raphe, as seen in olivopontocerebellar atrophy (Fig 3). In case 5, which was characterized by a mild degree of cerebellar atrophy and localized T2/FLAIR cortical hyperintensity, the pons remained normal at 2-year follow-up.

Supratentorial abnormalities involved the white matter in 2 cases. In case 1, myelination was delayed at age 11 months. In case 3, white matter volume loss and gliosis, corpus callosum atrophy, and cortical atrophy were found at presentation and significantly progressed on follow-up (Fig 3). Both patients had a significant degree of ventriculomegaly as a consequence of their supratentorial volume loss.

1H-MRS was interpretable in only 3 cases (cases 3, 4, 5), whereas quality was deemed insufficient in 1 (case 2) because of motion artifacts. The most significant finding consisted of reduced NAA/Cr ratios, which was particularly severe in cases 3 and 4, where the NAA peak was barely detectable (Fig 1); additionally, increased mIns was detected in 2 cases (cases 4, 5). In 1 case (case 4), prominent peaks at 3.36 and 3.8 ppm were found; these were automatically assigned to sI and the alpha-resonances of glutamine and glutamate, respectively (Fig 1).

Discussion
In CDG-1a patients, MR imaging typically shows a small cerebellum, variably designated as CH, olivopontocerebellar hy-
poplasia, and CA in the literature. Cerebellar MR spectroscopy findings have not been reported to our knowledge, though 1 report showed decrease in the NAA peak in supratentorial acute stroke regions.

Theoretically, the differentiation between CA and CH should be straightforward. CA is a progressive neurodegenerative condition in which an initially normal cerebellum displays progressive volume loss, with interfolial spaces eventually appearing larger than the folia. Conversely, CH is a congenital condition characterized by incomplete development of the cerebellum, in which the fissures are of normal size compared with the folia. In practice, such differentiation is much less easy to achieve, particularly when a single MR imaging study is available. In our series, all patients exhibited a variably severe volume loss of the cerebellum at presentation, with involvement of both the vermis and the cerebellar hemispheres, which further progressed on follow-up. Close scrutiny of vermian morphology revealed that, in most cases, the inferior vermis had a rudimentary, flattened appearance in the early stages, consistent with inferior vermis hypoplasia; on the other hand, atrophy became prominent in the superior vermis at later stages, but typically in the first 2 years of life. This suggests that neurodegeneration occurs early, when the external granule layer, which appears at the end of the embryonic period and persists up to 2 years after birth, is still playing an active germinal role and the development of the cerebellum is still incomplete. Thus, cerebellar involvement in CDG-1a is probably best described as a combination of CA and CH, similar to pontocerebellar hypoplasia and other putative prenatal-onset degenerative disorders.

A consistent, striking finding in our series was the presence of high T2/FLAIR signal intensity of the involved cerebellar cortex and, often, the subcortical white matter. To the best of our knowledge, this is a novel finding in CDG-1a, which we believe may be important in the differential diagnosis. In fact, CA is a nonspecific radiologic finding in children with a host of different causes, including genetic and acquired conditions, with different prognoses and, in some instances, therapeutic strategies; a pattern-recognition approach may therefore critically restrict the differential diagnosis and prompt specific laboratory and genetic studies. To this end, Poretti et al identified 5 subgroups of CA, namely, 1) isolated CA, comprising ataxia-telangiectasia, late-onset GM2 gangliosidosis, and ataxia-oculomotor apraxias; 2) CA and hypomyelination, including Pelizaeus-Merzbacher disease, Salla disease, leukoencephalopathy.

Fig 2. Evolution of findings in CDG-1a; case 1 at age 12 days (A and B) and 11 months (C and D). At presentation, sagittal T1-weighted image (A) shows mild hypoplasia of the inferior vermis (thin arrows); the pons and superior vermis appear normal. Coronal T2-weighted image (B) shows normal cerebellar hemispheres. At 11-month follow-up, sagittal T1-weighted image (C) shows considerable volume loss of the vermis. Notice, in particular, atrophic involution of the anterior lobe and declive (thick arrow), with corresponding fissural enlargement, whereas the inferior vermis retains a flattened appearance (thin arrow), with not so large fissures. The pontine protuberance is also diminished in size (arrowhead). Coronal T2-weighted image (D) also shows reduced size of both cerebellar hemispheres. The cerebellar cortex is hyperintense.
with ataxia, hypodontia and hypomyelination, and hypomyelination with atrophy of the basal ganglia and cerebellum; 3) CA and progressive white matter abnormalities, comprising neuronal ceroid lipofuscinoses, Niemann-Pick disease type C, dentatorubral-pallidolysian atrophy, vanishing white matter disease, and L2-hydroxyglutaric aciduria; 4) CA and basal ganglia involvement, including Kearns-Sayre syndrome and other mitochondrial disorders, Cockayne syndrome, Wilson disease, and 3-methylglutaconic aciduria; and 5) CA with cerebellar cortex hyperintensity. This latter category mainly comprises infantile neuroaxonal dystrophy, Marinesco-Sjogren syndrome, and mitochondrial disorders, other than acquired forms of CA, such as those following viral cerebellitis or exposure to exogenous toxic agents. We suggest that CDG-1a should also be included in the category of CA with cerebellar cortex hyperintensity; in such a context, a globally (rather than just cortical) hyperintense cerebellum in FLAIR, with evidence of volume loss in a patient presenting in the first 2 years of life, seems an important feature. In the absence of histologic verification, the cause of cerebellar hyperintensity remains speculative. We surmise a combination of astrogliosis, neuronal loss, and wrinkling of the cortex occurs, as suggested by $^1$H-MRS findings of reduced NAA/Cr and increased mIns concentrations that presumably reflect neuronal loss and astrogliosis, respectively.

Another important, albeit not constant, aspect in our series was represented by a small pontine protuberance. This finding was progressive in most cases, paralleling the progression of cerebellar volume loss and contradicting the increase in size that normally occurs during infancy. A small pons is a remarkable finding in the setting of CA, in that most hereditary forms of CA do not lead to significant brainstem atrophy, even in an advanced stage, with the notable exception of late-stage spinocerebellar ataxias and the group of pontocerebellar hypoplasias. The addition of CDG-1a to this group confirms that this is a form of early-onset neurodegenerative disorder.

The authors acknowledge that this study may be limited by intra- or interobserver variations due to our use of 2 unblinded observers to record all findings by consensus. Furthermore, standardized measurement techniques, including brainstem and cerebellar morphometry and ADC value determinations, could not be performed in all cases, which may have increased the risk of an inaccurate or biased interpretation of findings.

To summarize, our small sample of CDG-1a patients con-
sisted of children presenting, within the first 2 years of life, with variably severe but consistent MR imaging features of a small, hyperintense cerebellum, often associated with a small pons. This association seems to be peculiar in the large field of cerebellar atrophies and may prove useful in addressing the differential diagnosis by prompting specific laboratory tests, thereby saving time and costs. MR imaging findings, supported by 1H-MRS findings of reduced NAA/Cr and increased inositol resonances, support the hypothesis that CDG-1a is an early-onset neurodegenerative disorder in which cerebellar atrophy and hypoplasia coexist.

References