Early Features in Neuroimaging of Two Siblings With Molybdenum Cofactor Deficiency

abstract

We report the features of neuroimaging within 24 hours after birth in 2 siblings with molybdenum cofactor deficiency. The first sibling was delivered by emergency cesarean section because of fetal distress and showed pedal and crawling seizures soon after birth. Brain ultrasound revealed subcortical multicystic lesions in the frontal white matter, and brain MRI at 4 hours after birth showed restricted diffusion in the entire cortex, except for the area adjacent to the subcortical cysts. The second sibling was delivered by elective cesarean section. Cystic lesions were seen in the frontal white matter on ultrasound, and brain MRI showed low signal intensity on T1-weighted image and high signal intensity on T2-weighted image in bifrontal white matter within 24 hours after birth, at which time the infant sucked sluggishly. Clonic spasm appeared at 29 hours after birth. The corpus callosum could not be seen clearly on ultrasound or MRI in both infants. Cortical atrophy and white matter cystic lesions spread to the entire hemisphere and resulted in severe brain atrophy within ~1 month in both infants. Subcortical multicystic lesions on ultrasound and a cortex with nonuniform, widespread, restricted diffusion on diffusion-weighted images are early features of neuroimaging in patients with molybdenum cofactor deficiency type A. Pediatrics 2014;133:e267–e271
Molybdenum cofactor is a coenzyme common to sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase; and its deficiency leads to a phenotype that is quite similar to isolated sulfite oxidase deficiency (ISOD). Molybdenum cofactor deficiency (MoCoD) and ISOD are different rare diseases with autosomal recessive traits, but it is likely that severe encephalopathy in both diseases results primarily from sulfite oxidase deficiency. Two modes of presentation of MoCoD have been identified: early (classic) and late (atypical). Brain MRI has demonstrated cerebral infarction in classic MoCoD. Approximately 75% of cases with severe encephalopathy have been related to MoCoD.

Molybdenum cofactor is synthesized by a complex biosynthetic pathway that involves 4 steps. Two-thirds of patients with MoCoD lack cyclic pyranopterin monophosphate (cPMP) and are classified as having MoCoD type A. No effective therapy for this condition was available until recently, but successful treatment using cPMP has now been reported. This therapy should be started as early as possible to achieve favorable outcomes, which makes early diagnosis of MoCoD particularly important, although cPMP is not yet available for clinical use in Japan. Here, we report the neuroimaging features soon after birth in 2 siblings diagnosed with MoCoD type A.

PRESENTATION OF PATIENTS

Clinical Presentation

A 30-year-old primigravida delivered a male infant weighing 3942 g at a gestational age of 40 weeks and 0 days. Delivery was by emergency cesarean section due to loss of variability and no acceleration on a non–stress test. Apgar scores were 5 at 1 minute and 8 at 5 minutes; and thereafter, apnea and pedaling appeared and systemic cyanosis persisted. Pedaling and crawling seizures disappeared after administration of diazepam, phenobarbital, and midazolam. Multicystic lesions were seen in the frontal white matter with brain ultrasound, and hypoxic ischemic lesions were seen with brain MRI at 4 hours after birth.

Three years later, a second male infant weighing 3398 g was delivered by elective cesarean section at a gestational age of 37 weeks and 2 days since the first sibling had been delivered by emergency cesarean section. Apgar scores were 9 at 1 minute and 10 at 5 minutes. Multicystic lesions were seen in the frontal white matter on ultrasound and on MRI within 24 hours after birth, and the infant sucked sluggishly. Clonic spasm appeared at 29 hours after birth, for which phenobarbital and midazolam were administered. Spasm disappeared in 2 days but recurred 10 days after birth. At this time, oral carbamazepine was started instead of intravenous midazolam. Minor clonic seizure within 1 minute appeared on the face or on 1 or 2 extremities from time to time.

The diagnosis for the first sibling was hypoxic-ischemic encephalopathy (HIE). However, the second sibling was born uneventfully but also developed seizure, and brain ultrasound and MRI showed abnormalities similar to those in the first sibling. The first sibling has had a 3-year history of hypouricemia since 1 week after birth, and the second sibling also had hypouricemia on day 3. Gas chromatography–mass spectrometry analysis and a sulfite test (Merck, Darmstadt, Germany) indicated increased urinary excretion of hypoxanthine and xanthine, decreased urinary excretion of uric acid, and positive urinary sulfite (4+: SO$_4^{2-} = 400$ mg/L in the first sibling; 2+: SO$_3^{2-} = 80$ mg/L in the second sibling). We diagnosed MoCoD at 17 days after birth in the second sibling and as MoCoD type A on the basis of a homozygous c.1643C>A missense mutation found in exon 10 of the $MCS1$ gene in both infants in an analysis of the 4 genes related to molybdenum cofactor biosynthesis. The patients currently have microcephaly, severe spastic tetraplegia, and epilepsy lying inactively in bed and while swallowing food at the ages of 2 and 5 years old, respectively.

Neuroimaging in the 2 Siblings

An NICU pediatrician performed and evaluated brain ultrasound scans and evaluated MRI findings with the help of an experienced radiologist. Brain ultrasound revealed multiple cystic hyperechoic lesions in the frontal subcortical white matter and findings indicating corpus callosum dysgenesis in both infants within 24 hours after birth (Fig 1). Brain MRI in the first sibling showed hyperintense signals in almost the entire cortical area except for the right frontal lobe on diffusion-weighted imaging (DWI; b-value = 1000) and hypointensity on apparent diffusion coefficient maps, indicating restricted diffusion (Fig 2 A and B). A region of the cortex with low signal intensity on DWI (b-value = 1000) and high signal intensity on apparent diffusion coefficient maps extended from the right frontal lobe to the left frontotemporal lobe at 3.7 days after birth (Fig 2 D and E). At the same time, on fluid-attenuated inversion recovery (FLAIR) images, curvilinear high signal intensity was observed in between gray and white matter in the frontal lobe and spread to the whole hemisphere (Fig 2 C and F). This curvilinear high intensity was especially evident adjacent to subcortical cystic lesions with low signal intensity on FLAIR images (Fig 2 C).

Brain MRI in the second sibling showed low signal intensity on T1-weighted images (T1WIs) and high signal intensity signal on T2-weighted images (T2WIs) in the bifrontal subcortical
white matter and high signal intensity on T1WIs and low signal intensity on T2WIs in the basal ganglia and thalamus at 23 hours after birth (Fig 3 A and B). Atrophy in the cortex and central gray matter progressed, cystic lesions in the subcortical white matter spread, and severe brain atrophy resulted in 23 days (Fig 3 C, D, and E). The corpus callosum could not be seen on MRI in both infants.

**DISCUSSION**

Infants with classic MoCoD who present with intractable seizures in the newborn period have computed tomography and MRI findings reminiscent of those of HIE. Thus, early diagnostic clues for MoCoD in neuroimaging must be clearly understood to differentiate between these diseases and to perform early and appropriate treatment, because classic MoCoD progresses rapidly within 1 month, as shown in this report. Prenatal diagnosis has been made on the basis of sulfite oxidase activity or gene analysis in chorionic villi or amniotic cells. In a case with MoCoD type A diagnosed prenatally, sonography at 35 weeks' gestation revealed diffuse brain damage with multiple subcortical cavities, ventriculomegaly, dysgenesis of the corpus callosum, and a hypoplastic cerebellum with an enlarged cisterna magna. Multiple subcortical cavities were seen on ultrasound within 24 hours after birth in the 2 siblings in this report. Maternal-placental clearance of toxic substances such as sulfite may be effective until late pregnancy in the majority of cases but may not be effective in some cases.

A recent review of ISOD/MoCoD findings revealed that MRI initially shows extensive bilateral abnormal signal intensities suggesting edema of both gray and white matter with cytotoxic edema, and that edema subsequently decreases and curvilinear areas of reduced signal intensity appear at the gray/
white matter junction, suggesting hemorrhagic deposits and laminar necrosis. Veldman et al described 4 infants with MoCoD type A in whom no cysts, but edema, were observed on MRI in the first week of life. Abnormally high consumption of adenosine triphosphate (ATP) due to seizure results in neuronal energy failure and postictal edema, which appears as hyperintensity on DWI and may lead to laminar necrosis. To exclude the effects on MRI from seizure, the most common symptom in MoCoD or ISOD, MRI should be evaluated before seizure appears, as in the second sibling in this report, or before prolonged or repetitive seizure appears, as in the first sibling. Brain edema was not clear on FLAIR images or on T1WIs in these 2 infants. Accordingly, fetal distress, due to which emergency cesarean delivery was performed, and subtle seizures that appeared soon after birth are suspected to have been a chain of symptoms of MoCoD type A in the first sibling, although we initially diagnosed HIE on the basis of both observations.

DWI in MoCoD has a distinctive initial pattern of widespread restricted diffusion in the cortex at the depths of sulci over most of the right hemisphere and left frontal lobe, with relative sparing of the peripheral cortex, as revealed in an infant with MoCoD type B at age 27 days. In ISOD, restricted diffusion is also seen in almost the entire cortex and subcortical white matter, with posterior predominance on day 4. In our cases, the restricted diffusion area in the cortex tended to decrease at 3.7 days after birth in the first sibling, and cortical atrophy and subcortical leukoencephalomalacia followed in both infants. The onset of restricted diffusion in the entire cortex except for the region with subcortical cysts is thought to occur around birth, because the time course of the diffusion abnormality after perinatal hypoxic-ischemic brain injury reaches a nadir after 2 to 3 days and pseudo-normalizes after 7 days. In addition, the cortex area near the cysts did not show restricted diffusion; therefore, the insult to areas with subcortical cysts is thought to start before birth. Neuropathological findings of cortical necrosis and extensive cavitating leukoencephalopathy were reminiscent of those in severe perinatal asphyxia, suggesting an etiology of energy deficiency in MoCoD and ISOD. The sulfite oxidase enzyme is located in the mitochondrial intermembranous space and is involved in electron transfer from sulfites into the electron transport chain. Exposure of rat and mouse neuronal cell lines to sulfites in vitro results in an increase in production of reactive oxygen species and reduced intracellular ATP production. Insult by sulfite may appear depending on the area and timing of higher ATP consumption in infants, that is, in gray matter rather than in white matter and at birth rather than before birth.

The nonuniform distribution of restricted diffusion in the cortex area in the hemisphere shown in the current report has also been noted previously. On the DWI pattern, restricted diffusion was not seen after birth in the left frontal lobe in the first sibling, in both frontal lobes in the previous report, and in the left occipital lobe in the recent report. The nonuniform distribution of restricted diffusion may reflect local differences in chronicological change in cortical injury by sulfite because the cortex area adjacent to subcortical cysts did not show restricted diffusion and also may be a feature of diagnostic imaging of MoCoD or ISOD. In contrast, hypoxic-ischemic insult starts in all regions at the same time, and an increased signal is seen throughout all cortical and subcortical areas.

**FIGURE 3**

Coronal sections of brain MRI in the second sibling at 23 hours (upper row) and 24 days (lower row) after birth. A and B, Multiple subcortical cystic lesions with low signal intensity on T1WIs and high signal intensity on T2WIs were seen in both frontal lobes at 23 hours. High signal intensity on T1WIs and low signal intensity on T2WIs were observed in the globus pallidus and thalamus. C–E, These cysts spread to the entire hemisphere, and gray and white matter decreased in volume after 23 days. High signal intensity on T1WIs and FLAIR images and low signal intensity on T2WIs remained in the cortex of the frontal and posterior lobes at 24 days after birth. Agenesis of the corpus callosum was suspected on the basis of the findings in the lateral ventricles similar to those in the first sibling.
areas (referred to as a “white cerebrum” in severe cases) on DWIs recorded within 1 week after birth.

Agenesis or hypoplasia of the corpus callosum was described in 5 (type A; 1; type unknown: 4) of 12 cases of MoCoD in Turkey as well as in infants with ISOD and was also seen in both infants in this report. Dysgenesis of the corpus callosum has a heterogeneous etiology and may be associated with metabolic disorders of organic acids, such as propionic acidemia or pyruvate dehydrogenase complex deficiency. Thus, MoCoD and ISOD should be viewed as a metabolic disorder that may be associated with dysgenesis of the corpus callosum. Subcortical multiple cysts on ultrasound and nonuniform restricted diffusion in the cortex on DWI soon after birth are early imaging findings that suggest MoCoD type A.

Neonates with MoCoD and those with HIE show early-onset seizures. However, those with MoCoD have low plasma uric acid, positive sulfite dipstick in fresh urine, and elevated urine and plasma s-sulfocysteine; whereas those with HIE do not have any of these markers and have elevated plasma uric acid. On DWIs taken within 1 week after birth, an increased signal is seen throughout all cortical and subcortical areas in patients with HIE but nonuniformly in cortical and subcortical areas in those with MoCoD.

REFERENCES

Early Features in Neuroimaging of Two Siblings With Molybdenum Cofactor Deficiency
Ryuzo Higuchi, Takuya Sugimoto, Akira Tamura, Naomi Kioka, Yoshinobu Tsuno, Asumi Higa and Norishige Yoshikawa
*Pediatrics* 2014;133;e267; originally published online December 30, 2013; DOI: 10.1542/peds.2013-0935

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: /content/133/1/e267.full.html</th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td>This article cites 16 articles, 5 of which can be accessed free at: /content/133/1/e267.full.html#ref-list-1</td>
</tr>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s): Administration/Practice Management /cgi/collection/administration:practice_management_sub Medical Technology and Advancement /cgi/collection/med_tech_advancement_sub Genetics /cgi/collection/genetics_sub Epigenetics /cgi/collection/epigenetics_sub</td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: /site/misc/Permissions.xhtml</td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: /site/misc/reprints.xhtml</td>
</tr>
</tbody>
</table>
Early Features in Neuroimaging of Two Siblings With Molybdenum Cofactor Deficiency
Ryuzo Higuchi, Takuya Sugimoto, Akira Tamura, Naomi Kioka, Yoshinobu Tsuno, Asumi Higa and Norishige Yoshikawa

Pediatrics 2014;133:e267; originally published online December 30, 2013;
DOI: 10.1542/peds.2013-0935

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/133/1/e267.full.html