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Dilated Perivascular Spaces: An Informative Radiologic Finding in Sanfilippo Syndrome Type A

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Mucopolysaccharidosis type IIIA, or Sanfilippo syndrome type A, is a lysosomal storage disorder caused by deficiency of heparan *N*-sulfamidase, resulting in defective degradation and subsequent storage of heparan sulfate. It is characterized by progressive nervous system involvement. Cribriform changes in the corpus callosum, basal ganglia, and white matter, diffuse high-intensity signal in the white matter, and cerebral atrophy have been described in patients with this disorder. This case report describes a child with Sanfilippo syndrome type A who exhibited fairly mild clinical findings but an unusual magnetic resonance imaging pattern that included multiple moderate-sized cysts (probably enlarged perivascular spaces) within the corpus callosum and an abnormal appearance of the clivus and cervical vertebrae. This case calls attention to the variety of appearances possible with magnetic resonance imaging in Sanfilippo syndrome type A.

Kara S, Sherr EH, Barkovich AJ. Dilated perivascular spaces: an informative radiologic finding in Sanfilippo syndrome type A. Pediatr Neurol 2008;38:363-366.

Introduction

Mucopolysaccharidosis type III, or Sanfilippo syndrome, is an autosomal recessive inherited disease caused by lack of degradation of heparan sulfate in lysosomes. In the most common subtype (type IIIA), deficiency of sulfamidase (*N*-sulfoglucosamine sulfohydrolase, EC 3.10.1.1; also known as heparan *N*-sulfatase) results in lysosomal storage of heparan sulfate and leads to severe neurodegeneration. Affected patients develop progressive dementia (often including rapid loss of social skills, mental decline, delayed speech, and disturbed sleep patterns), hirsutism, coarse facies, diarrhea, hyperactivity, aggressive behavior, and gait disturbances; ultimately, the result is early death. The skeletal pathology is relatively mild, and often develops after the diagnosis is established. Joint stiffness and hepatosplenomegaly are found mostly in older patients [1-5].

The incidence of mucopolysaccharidosis type III subtypes ranges from 1:20,000 to 1:324,000 in different geographic regions but mucopolysaccharidosis type IIIA is the most common type in northern Europe and Australia. Clinical onset in severely affected mucopolysaccharidosis type IIIA patients usually comes after 2 to 3 years of apparently normal development. In less severe cases, the diagnosis may be missed because of the mild somatic and radiologic features, and because of false-negative findings in urine screening for elevated heparan sulfate [3-7].

The first imaging studies of central nervous system involvement of mucopolysaccharidoses were done with x-ray computed tomography. Because the findings were nonspecific (low-density areas in the white matter with dilation of ventricles and subarachnoid spaces [2,8]), magnetic resonance imaging has become the primary imaging technique for the detection of central nervous system abnormalities. Hyperintense white matter lesions, dilated perivascular spaces, atrophy, hydrocephalus, cystic cribriform changes in white matter, subtle cerebellar atrophy, dilatation of venous sinuses, thickening of the diploë, and spinal canal stenosis have been described. However, the severity of the magnetic resonance imaging findings is unrelated to the severity of the clinical phenotype [9]. Such was the case with the present patient, who had fairly severe magnetic resonance imaging findings despite a relatively mild clinical course.

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Received October 18, 2007; accepted January 21, 2008.

doi:10.1016/j.pediatrneurol.2008.01.009 • 0887-8994/08/$—see front matter

Case Report

This 5-year-old boy, the product of an uncomplicated full-term pregnancy and delivery, had normal early development. By age 2½, however, there were concerns about development difficulties (particularly lack of language acquisition), and in the last 6 months prior to presentation at our clinic the patient showed true regression.

On physical examination, the patient's weight and height were both at approximately the 75th percentile. His head circumference was greater than the 95th percentile for his age. He showed mildly dysmorphic craniofacial features, with evidence of frontal bossing, supraorbital ridging, and thickened eyebrows with borderline synophrys. He had also thickened features in his jaw, nose, and lips. Review of a photograph taken six months earlier documented increased coarsening of his features. The abdomen was soft without hepatosplenomegaly, but a small umbilical hernia was present. The patient had some loose stools, but the test for celiac disease was negative. The review of his other organ systems was unremarkable.

The patient had no seizures or abnormal movements. There was no evidence of neurologic complications by report. On neurologic examination, he was awake, alert and anxious. He had mild language disability, without motor dysfunction. There was no corneal clouding. Motor examination revealed normal bulk, tone, and power in all four extremities. Deep tendon reflexes were 2+/4 and symmetric. Plantar responses were equivocal. Gait testing revealed bilateral genu varum that appeared to be orthopedic in nature. Sensory examination revealed grossly intact functions.

Magnetic resonance imaging showed small perivascular spaces in the bilateral retrotrigonal, frontal, and subinsular regions, in addition to multiple cysts (isointense to cerebrospinal fluid and, therefore, likely representing dilated perivascular spaces) within the body of the corpus callosum and the adjacent white matter. The corpus callosum was thin posteriorly, with a small, short splenium. Regions of hyperintensity were seen on T_2-weighted and fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging in the subcortical white matter of the frontal and temporal lobes. Subarachnoid spaces and ventricles were enlarged. There was increased thickening of diploic spaces of the calvarium. The basisphenoid bone was widened and coarse in appearance, with abnormal-appearing marrow. The dens was extremely hypoplastic, and the other upper cervical vertebrae were short and dysmorphic (Fig. 1a-d).

His urinalysis showed a mucopolysaccharide screen level of 51.9 mg/mM (five-fold increase above normal) and revealed elevation of heparan sulfate on thin-layer chromatography. Assay of cultured skin fibroblasts established a deficiency of sulfamidase and confirmed the diagnosis of Sanfilippo syndrome type A.

Discussion

Sanfilippo syndrome is reported to have subtle magnetic resonance imaging findings early in the course of the disease. In the present case, however, the patient had only mild clinical manifestations of the disease, and the magnetic resonance imaging findings were the key to establishing the correct diagnosis. Neither the presentation nor the physical exam early on suggested a mucopolysaccharidosis as the diagnosis. In profoundly affected patients, delayed development is often noticed at 2 to 3 years of age, severe neurologic deterioration occurs by 6 to 10 years of age, and most die before age 20 years. Mucopolysaccharidosis type IIIA has earlier and more severe clinical manifestations, with an earlier age at death than types IIIB and IIIC. There are also reports of interfamilial and intrafamilial variability within each subtype. This may be caused by both genetic and environmental factors [3].

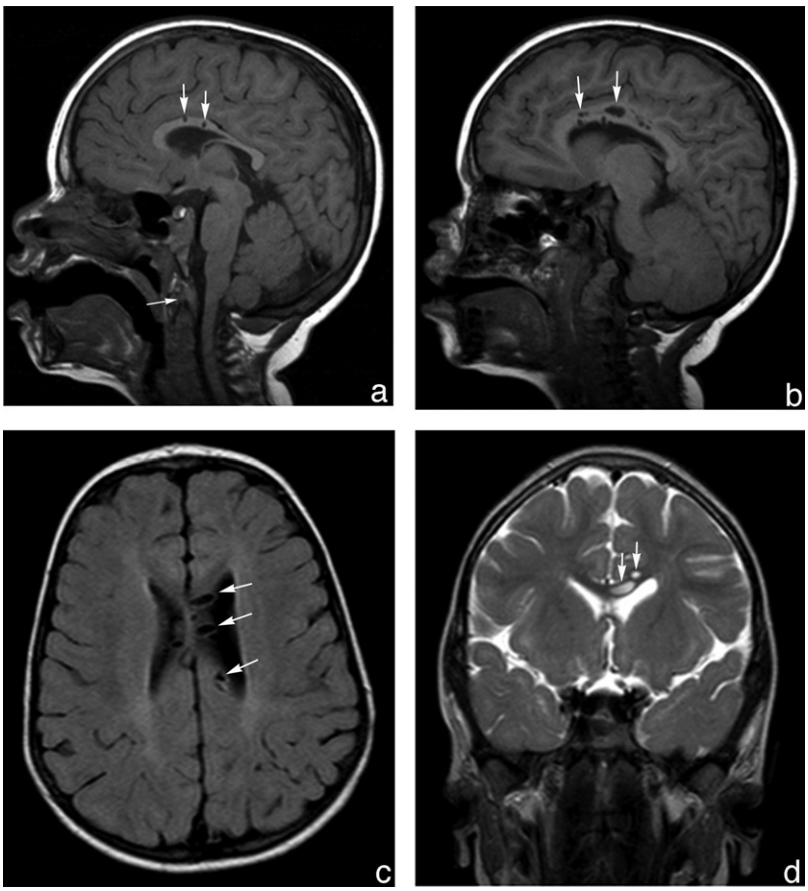

Figure 1. (a, b). Sagittal T_1-weighted (TR/TE = 600/15 ms) images demonstrate involvement of the corpus callosum by dilated perivascular spaces (large white arrows). The corpus callosum was thin posteriorly, with a small, short splenium. The odontoid (small white arrow) is extremely hypoplastic. Signal intensity of cervical vertebral bodies is hypointense, and therefore the intervertebral disks cannot be differentiated from the vertebral bodies. The clivus is abnormally vertical, with hypointense signal intensity. The sella turcica is shallow. (c) Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (TR/TE = 10,000/100 ms) demonstrates several cyst-like dilated perivascular spaces (arrows) in the body of the corpus callosum. The signal intensity of the fluid within the cysts was isointense to cerebrospinal fluid in all sequences. (d) Coronal T_2-weighted (TR/TE = 2500/80 ms) image demonstrates abnormally hyperintense signal of the subcortical white matter in the frontal and anterior-superior temporal lobes. Arrows indicate cystic changes (hyperintense signal) present in the body of the corpus callosum.

The mucopolysaccharidoses lead to the accumulation of glycosaminoglycan in many tissues. Neuropathologic studies of the central nervous system have demonstrated ceroid lipofuscin storage and variable amounts of zebra bodies and of membranogranulovacuolar inclusions in the brains of affected patients. The mucopolysaccharidosis type IIIA cases contain larger amounts of zebra bodies, but these are a nondistinctive feature between types [10,11]. Enlarged perivascular spaces have been noted, presumably secondary to mucopolysaccharide accumulation, in addition to demyelination and gliosis in the white matter.

It has been postulated that, during the natural course of mucopolysaccharidosis, enlarged perivascular spaces develop first, followed by white matter changes and then, lastly, atrophy. It has been further suggested that dilated perivascular spaces in the white matter and corpus callosum may suggest a poorer prognosis, and that the optimal time for therapeutic intervention may be early, when the cysts are still relatively small and few [12]. No correlation between the severity of the alterations of white matter and the mucopolysaccharidosis type or the patient's age has been shown.

Magnetic resonance imaging of the present patient showed multiple cystic lesions, but the white matter changes and atrophy were not particularly remarkable at the time of the scan, showing foci of T_2 and FLAIR hyperintensity primarily in the frontal and temporal lobes. Similar white matter changes have been described and are postulated to be the result of delayed myelination, gliotic response to mucopolysaccharide deposition, or glycosaminoglycan or lipid accumulation in neurons or perivascular spaces [13].

Although the enlarged perivascular spaces in the corpus callosum, as here described, are not frequently reported in Sanfilippo type A, this finding has been well described for other mucopolysaccharidoses. Gabrielli et al. [11] first showed cribriform small cystic alterations in the white matter; these have been described as pathognomonic findings for mucopolysaccharidoses by some authors. The cystic changes are localized mainly in the periventricular white matter, the corpus callosum and the basal ganglia, with diameters ranging from 2 to 8 mm. These are most severe in children with Hunter's syndrome or Hurler's syndrome, but the size and extent of the cystic changes do not correlate with severity of mental retardation [12]. If the cystic areas are, indeed, caused by deposition of mucopolysaccharides in perivascular spaces, there is no reason why such cysts could not develop in any of the mucopolysaccharidoses; therefore, a diagnosis of mucopolysaccharidosis, regardless of type, should be considered whenever these imaging findings are noted.

Ventricular dilatation and enlargement of subarachnoid spaces are also considered common findings in mucopolysaccharidosis type III; they are generally considered to represent a combination of atrophy and hydrocephalus, the latter most likely resulting from increased venous pressure due to reduced outflow through the abnormal skull base. Hydrocephalus can be an important cause of morbidity in mucopolysaccharidosis type III, because chronic intraventricular high pressure can lead to behavioral disturbances and damage to the optic nerves and brainstem [13,14]. Neurosurgical intervention may be recommended in such patients. In the present case, only mild enlargement was seen.

Mucopolysaccharidosis causes anomalous vertebral development and can result in spinal stenosis, with resulting cervical myelopathy. In addition, spinal cord injury may develop at the craniocervical junction, caused by odontoid hypoplasia and $C_{1\text{-}2}$ instability; further damage may result from stenosis at that level secondary to formation of a pseudotumor by ligamentous hyperplasia and intradural mucopolysaccharide deposition [2,15]. In the present case, the basisphenoid portion of the clivus was noted to be coarse and thickened. The odontoid was small, the cervical vertebrae were short in their superior–inferior dimension and were separated by enlarged intervertebral disks, and the spinal canal was narrowed. The patient did not yet, however, have any symptoms of spinal stenosis.

Conclusions

Magnetic resonance imaging findings raised the possibility of mucopolysaccharidosis in a patient with nonspecific developmental delay and mildly dysmorphic features. Cystic changes (dilated perivascular spaces) in the corpus callosum, basal ganglia, and white matter on magnetic resonance imaging should raise the possibility of a mucopolysaccharidosis, especially if seen in association with high-intensity signal in the white matter on T_2-weighted images, enlargement of supratentorial external cerebrospinal fluid spaces, ventriculomegaly, diffuse cerebral cortical atrophy, and spinal stenosis.

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