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Neuroradiologic Findings in Fucosidosis, a Rare Lysosomal Storage Disease

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Summary: Fucosidosis is a rare lysosomal storage disorder with the clinical features of mental retardation, cardiomegaly, dysostosis multiplex, progressive neurologic deterioration, and early death. The neuroradiologic findings in two patients are reported, and include abnormalities within the globus pallidus (both patients) and periventricular white matter (one patient).

Index terms: Brain, metabolism; Degenerative disease, Pediatric neuroradiology

Fucosidosis is a rare metabolic disorder caused by decreased amounts of the enzyme α-L-fucosidase, which results in the accumulation of fucose-rich storage products within many organs, including the brain. Patients with this disorder usually have delayed intellectual and motor development, and often die within the first decade of life. Computed tomographic (CT) findings have been reported in a few cases (1, 2).

Case Reports

Case 1

Seizures developed in a 10-year-old girl with a history of severe developmental delay. She was the product of an uncomplicated full-term pregnancy, and weighed 2688 kg at birth. She was thought to be healthy at birth, with normal early motor development, but the onset of toe-walking occurred later. She never developed expressive language. The family history was significant for a maternal uncle with short stature and mental retardation who died at the age of 14 years.

Physical examination demonstrated coarsened facial features, bilateral horizontal gaze nystagmus, short stature, prominent lumbar lordosis, and hepatomegaly. A 4 × 1.5-cm red coarse patch present since birth, consistent with an angiokeratoma, was identified on the trunk. Abnormal laboratory findings included an extremely low α-L-fucosidase level in fibroblasts and plasma. Electron microscopy examination of a skin biopsy revealed partially vacuolated secondary lysosomes containing some fine fibrillar material and lamellated membrane structures.

A magnetic resonance (MR) examination at the age of 10 years showed confluent regions of hyperintense signal on T2-weighted images in the periventricular regions, most prominent surrounding the atria of the lateral ventricles. Hyperintense signal was noted in the globus pallidus on T1-weighted images, with corresponding hypointense signal on T2-weighted images (Fig 1).

Case 2

A 2-year-old boy was examined for speech delay and psychomotor retardation. He was born at term after a normal pregnancy, and appropriate development occurred during the first year of life. However, by age 2 years, the patient had not developed speech, exhibited autistic behavior, and performed motor tasks poorly. Physical examination findings included coarsened facial features, narrow, wide-spaced teeth, a large cutaneous hemangioma on one thigh, and clumsy gait. Radiographs of the spine showed anterior, inferior beaking of the lower thoracic and upper lumbar vertebral bodies. Cranial CT examination showed bilateral low-attenuation regions within the globus pallidus (Fig 2), with an otherwise normal examination. Low α-L-fucosidase levels within serum and homogenized leukocytes were demonstrated.

Discussion

Fucosidosis is a rare inborn error of metabolism caused by deficiency of α-L-fucosidase, a lysosomal enzyme that hydrolyzes fucose from several biological substrates (3). Fucosidosis is classified as a lysosomal storage disorder. Lysosomes are membrane-bound vesicles containing hydrolytic enzymes (such as proteases, phosphatases, glycosidases, lipases, and nucleases) that function in digesting intracellular and extracellular substances. Lysosomes are found in most cells, but are particularly abun-

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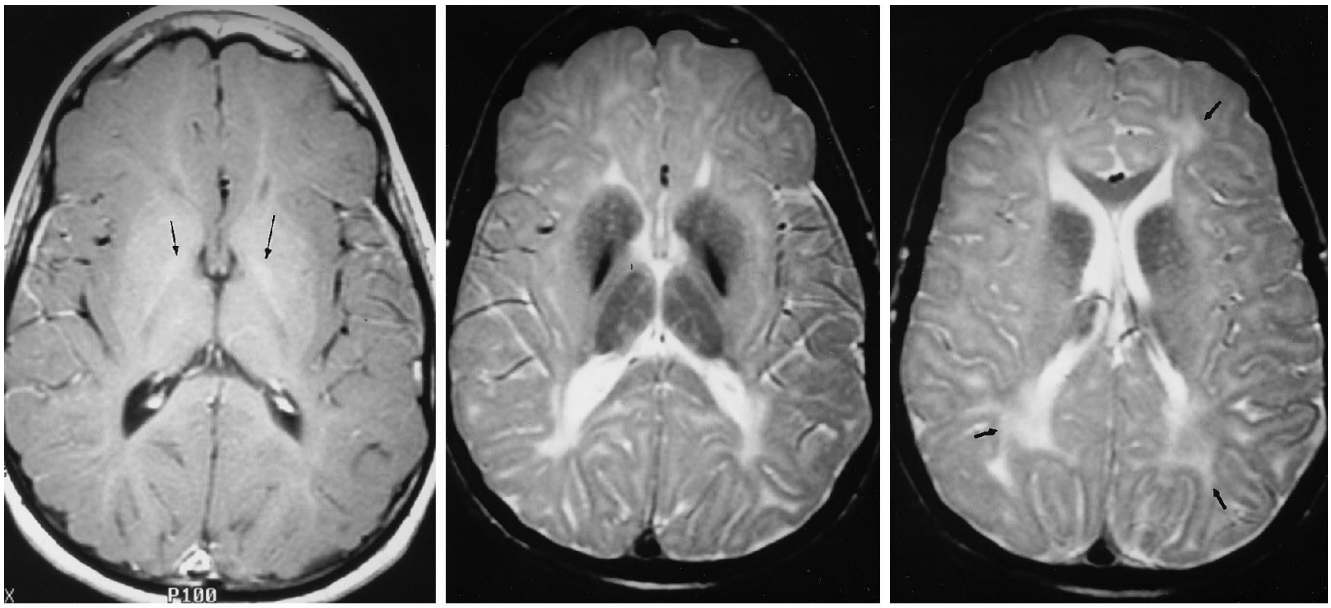


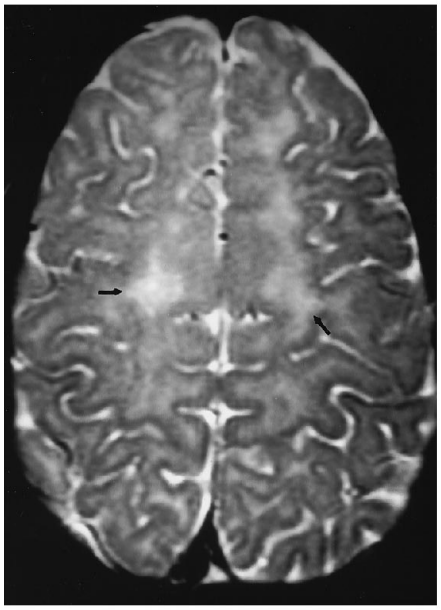
Fig 1. Case 1, 10-year-old girl.

A, Contrast-enhanced T1-weighted axial MR image (700/11/2 [repetition time/echo time/excitations]) shows hyperintense signal within the basal ganglia bilaterally (*arrows*). The signal intensity was unchanged from noncontrast images.

B, T2-weighted axial MR image (2200/80/1) shows very hypointense signal within the globus pallidus.

C, T2-weighted axial MR image. Hyperintense signal abnormality is seen in the periventricular regions (*arrows*).

D, T2-weighted axial MR image. The hyperintense signal abnormality extends into the subcortical white matter (*arrows*).



dant in phagocytic cells, where they are important in the digestion of phagocytosed materials. The main categories of lysosomal storage diseases are the sphingolipidoses, glycoproteinoses, glycogen storage diseases, mucolipidoses, and the mucopolysaccharidoses. Fucosidosis is one of the glycoproteinoses, along with sialidosis, mannosidosis, and aspartylglycosaminuria. Fucose is a hexose sugar that is a component of many mucolipids, mucopolysaccharides, and glycoproteins. The deficiency of α-L-fucosidase results in accumulation of a variety of fucose-rich glycoproteins, glycolipids, and mucopolysaccharides within lysosomes of cells of most organs, including liver, spleen, kidney, heart, brain, peripheral nerves, and skin (4).

Two main forms of fucosidosis have been recognized. Patients with type I fucosidosis present in early infancy with developmental delay and psychomotor retardation. Cardiomegaly, hepatomegaly, and hyperhidrosis are commonly seen. The clinical course in these patients is one of rapidly progressive neurologic deterioration to a decerebrate state and death

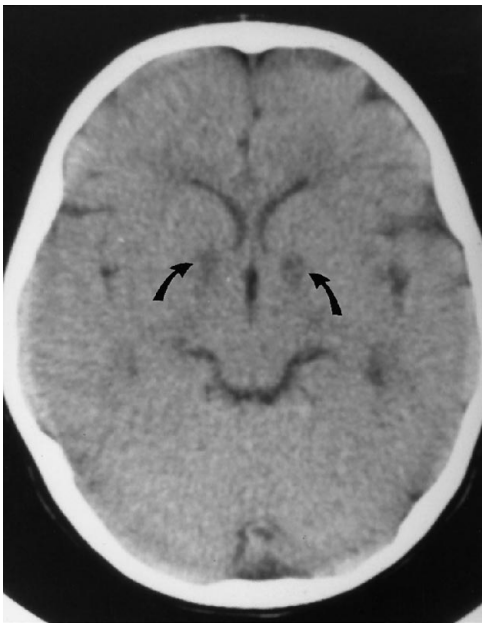


Fig 2. Case 2, 2-year-old boy. Noncontrast CT examination shows bilateral low-attenuation abnormalities in the globus pallidus (*arrows*).

before the age of 5 years (4). Type II disease is characterized by late infantile onset, short stature, coarse facies, mental retardation, hypertonia, confluent skin lesions termed angiokeratoma corporis diffusum, and longer survival than type I. It is becoming clear, however, that a disease spectrum exists, with some cases having features of both subtypes (5). Two thirds of patients survive into the second decade (5), but survival past the age of 30 is rare (2). The mode of transmission is thought to be autosomal recessive (3). Clusters of the disease are seen within a few ethnic groups. A large percentage of the reported cases of fucosidosis are found in either southern Italy or the Mexican-Indian population of the western United States (5).

Cutaneous or visceral abnormalities are seen in almost half of cases. The most notable cutaneous finding is angiokeratoma corporis diffusum, tiny purple or red raised cutaneous lesions that are initially found on the trunk but progress to cover most of the body. These are seen in about one half of patients and are found in increased numbers in older patients (5). They are thought to be secondary to the accumulation of fucose-rich oligosaccharides and glycoproteins within endothelial cells and fibrocytes (3). Although this finding is helpful in the diagnosis, it is nonspecific, as it is also seen in two unrelated diseases, α-galactosidase A deficiency (Fabry disease) and sialidosis (5). Accumulation of abnormal lysosomal storage products, primarily glycoproteins and glycolipids, within the viscera is also a common finding (7). This results in mild, nonprogressive hepatomegaly in approximately 40% and splenomegaly in 25% of patients (5). Microscopic examination of splenic and liver parenchymal cells shows swollen cells with clear vacuoles that are surrounded by a membrane (5). Similar findings are seen within cardiac muscle, which results in the cardiomegaly seen in type I disease (4).

The disease can be diagnosed by a number of different means, including determination of low α-L-fucosidase activity in plasma, urine (3), cultured skin fibroblasts, or peripheral leukocytes (5); detection of urinary oligosaccharides and glycopeptides; and rectal biopsy (2). Prenatal diagnosis by measurement of enzyme activity in amniotic fluid and cultivated amniotic fluid cells is also possible. A mutation in the structural gene encoding α-L-fucosidase has been identified in patients with either form of the disease (6).

Reported neuropathologic findings include prominent neuronal loss within gray matter structures, especially in the thalamus, hypothalamus, cerebral cortex, Purkinje cells, and dentate nucleus (4). Nerve cell bodies are distended and appear empty or filled with a slightly basophilic material. Although the cells usually appear vacuolated, unusual lamellated fibrillogranular intracellular inclusion bodies can also seen, possibly because of accumulation of glycolipids (5). Prominent white matter demyelination or dysmyelination, with severe damage to myelin sheaths and depletion of oligodendroglia, has been reported (4, 7). Large amounts of macrophages laden with triglycerides, neutral fats, and cholesterol esters within the globus pallidus have been reported in one case (7). These lesions may be an indirect effect of α-L-fucosidase deficiency, and produced by increased activity of other lysosomal enzymes in response to the deficiency.

Various radiologic findings involving the skeleton can be seen. The most common is dysostosis multiplex, which predominantly affects the spine, pelvis, and hips. The lower thoracic and lumbar vertebrae are flattened and are beaked anteriorly (8). In addition, the diaphyses of the long bones are widened, scalloped, and sclerotic, and there is acetabular widening and flar-

ing of the iliac bones (8). Skeletal maturation is usually delayed.

Reports of cranial CT findings in patients with fucosidosis are sparse. Diffuse, severe cerebral and cerebellar atrophy has been reported in the few published cases (1, 2). Although cerebral and cerebellar atrophy was not demonstrated in our patients, this may reflect the young ages of our patients (significantly younger than those for which CT findings have been reported). Focal low-attenuation regions within the corona radiata extending up to the subcortical white matter, in the same distribution as the hyperintense periventricular abnormalities seen on T2-weighted images in our first patient, have been described (1). These findings may represent white matter regions of demyelination and gliosis in areas where the neuronal loss is most severe (4, 7). Similar white matter findings have been reported in a number of other lysosomal storage diseases, including the sphingolipidoses (eg, metachromatic leukodystrophy, GM_1 gangliosidosis, and Krabbe disease) and mucopolysaccharidoses (9–12), as well as mannosidosis, another form of glycoproteinosis (13). The white matter signal abnormalities in these disorders have been presumed to result from the effects of intracellular storage products (ie, demyelination, gliosis, and possibly edema) rather than from prolonged T2 relaxation properties of the storage products themselves (10, 11, 13).

Abnormalities of the globus pallidus on both CT and MR imaging were the other major findings in our patients. These findings have not been previously reported in this disease (1, 2). Except for the sole report of macrophages laden with triglyceride, neutral fats, and cholesterol esters within the globus pallidus in a single patient (7), there are no other reports of neuropathologic abnormalities in the globus pallidus. Basal ganglia abnormalities have been reported in a number of other lysosomal storage diseases, including low-attenuation abnormalities on CT (with corresponding hyperintense signal abnormalities on T2-weighted MR images) in mucopolysaccharidosis type II (11). High-attenuation abnormalities on CT examination have been demonstrated in Krabbe disease, although they appear to predominate in the thalami and periventricular white matter (10, 12).

The cause of the globus pallidus abnormalities in the two patients presented here is not known with certainty. The presence of macrophages containing cholesterol, triglycerides, and fat within the globus pallidus, as was reported in a single fucosidosis patient (7), could produce T1 shortening, but would not be expected, in itself, to produce the hypointense signal on T2-weighted images seen in case 1. Although subacute hemorrhage would result in a hyperintense appearance on T1-weighted images with a hypointense appearance on T2-weighted images, bilateral symmetric hemorrhage is unlikely. Although calcification could potentially produce this combination of MR findings, there was no evidence of calcification on the CT examination performed in case 1 four years before the MR examination. Furthermore, the CT examination performed in case 2 show low- (rather than high-) attenuation globus pallidus abnormalities and no evidence of calcification.

There is currently no treatment for the neurologic or other systemic manifestations of fucosidosis. On the basis of successful use of allogeneic bone marrow transplantation to treat other metabolic disorders, this form of treatment has been attempted in a canine model of fucosidosis. These dogs experience progressive ataxia, proprioceptive dysfunction, dysphagia, and wasting, and are found to have lowered α-L-fucosidase levels in leukocytes and cultured fibroblasts (14). Bone marrow transplantation in these dogs has resulted in elevation of central nervous system levels of fucosidase, reduction in severity of central nervous system storage lesions, and failure to develop the expected severe neurologic signs of the disease when transplantation is performed before the animals have matured (14).

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