MR Brain Imaging of Fucosidosis Type I

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Summary: Fucosidosis is a rare autosomal recessive lysosomal storage disease with the main clinical findings of progressive neuromotor deterioration, seizures, coarse facial features, dysostosis multiplex, angiokeratoma corporis diffusum, visceromegaly, recurrent respiratory infections, and growth retardation. Fucosidosis type I rapidly evolves toward a progressive neurologic deterioration and death. We report MR imaging findings of the brain of three patients with fucosidosis type I, including previously unreported findings, to expand the knowledge of the neuroradiologic spectrum of the disease.

Fucosidosis is a rare autosomal recessive lysosomal storage disease caused by the deficiency of lysosomal enzyme α-L-fucosidase, the enzyme that hydrolyzes fucose from glycolipids and glycoprotein. This results in the accumulation of a variety of α-L-fucose-rich storage products in many organs, such as liver, spleen, skin, heart, pancreas, thymus, thyroid, and kidneys, as well as the brain (1–4). The storage material consists largely of glycoasparagines (glycoproteins), and to a lesser extent, oligosaccharides, mucopolysaccharides, and glycolipids (1–6). The locus for α-L-fucosidase has been assigned to chromosome 1 at position 1p34.l–36.1, and is designated FUCA1 (3). Two clinical variants have been described (2–10). Fucosidosis type I is characterized by early mental and motor regression with rapidly progressive neurologic deterioration to a decerebrate state and death in the first decade of life (1–6). The facial appearance may resemble that seen in mucopolysaccharidosis. Cardiomegaly, hepatomegaly, and anhydrosis are commonly seen. Fucosidosis type II has a milder and more prolonged course, and affected patients

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often reach adulthood (4–6, 10, 11). Clear-cut distinction between the two types may be complicated by the occurrence of both within one family (2–4). The demonstration of the deficiency of α-L-fucosidase in urine, leukocytes, cultured fibroblasts, or other tissues permits a definite diagnosis.

The purpose of this report is to present the MR imaging findings of the brain of three patients with fucosidosis type 1. Some of these findings are similar to those previously described (5–9), whereas others are newly reported, involving the hypothalamus, putamen, and medullary laminae of the globi pallidi.

Case Reports

The clinical findings of the three patients are summarized in the Table. In all of them, abnormal oligosaccharide urinary levels, and markedly (patient 1) or undetectable (patients 2, and 3) α-L-fucosidase activity on peripheral leukocytes permitted the diagnosis.

Patient 1

MR imaging of the brain at 0.5 T showed extensive, confluent, and symmetrical signal alteration of the cerebellar, cerebral periventricular, lobar, and subcortical white matter as well as of the internal, external, and extreme capsules, which appeared hyperintense on T2-weighted images. Globi pallidi showed high signal intensity on T1-weighted images and low signal intensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images. T2-weighted images showed a subtle hyperintensity in the internal medullary laminae of the thalami. Two curvilinear streaks of low signal intensity on T1-weighted images and increased signal intensity on T2-weighted and FLAIR images were evident within the lentiform nucleus bilaterally, corresponding to the lateral and medial medullary laminae of the globi pallidi. Both putamina were hyperintense on T2-weighted and FLAIR images.

Patient 2

MR imaging of the brain at 1.5 T showed extensive, confluent, and symmetrical signal alteration of the corpus medullare; the periventricular, lobar, and subcortical white matter; the internal, external, and extreme capsules; and the internal medullary laminae of the thalami, which appeared hyperintense on T2-weighted images (Fig 1). T1-weighted images showed relatively high-signal globi pallidi with a hypointense streak between medial and lateral segments of the globi pallidi. On T2-weighted images, this curvilinear streak was hyperintense and the globi pallidi presented abnormal low signal intensity. High signal intensity was evident also in the putamina and in the hypothalamus. MR imaging of the thoracolumbar spine showed anterior and posterior vertebral beaking (Fig 1F).

Patient 3

MR imaging of the brain at 1.5 T showed diffuse, confluent, and symmetrical signal alteration of the corpus medullare as

Demographics and clinical findings in three patients with fucosidosis type I

Patient, Sex, Age at Presentation, Parents, Type of Pregnancy	Presenting Findings	Physical Examination	Neurologic Findings	EEG
1, male, 26 months, healthy non-consanguineous Italian parents, uncomplicated full-term	Progressive neuromotor and speech delay, recurrent respiratory infections	Mild facial dysmorfism, moderate splenomegaly, catarrhal cough	Spastic quadriplegia, Babinski sign, dysmetria, tremors	Abnormal
2, female, 2½ years, healthy non-consanguineous Italian parents, uncomplicated full-term	Progressive neurological deterioration, seizures	Macrocephaly, mild facial dysmorphism, kyphoscoliosis, hepatomegaly, abdominal and genital telengiectasias	Spastic quadriplegia, Babinsky sign, motor and mental impairment	Abnormal
3, male, 2 years, healthy non-consanguineous Italian parents, normal pregnancy as first product of fertilization in vitro and embryo transfer-FIVET	Psychomotor retardation, hearing loss, recurrent respiratory infections	Coarsened facial features, macrocephaly, facial teleangiectasias, catarrhal cough, umbilical hernia, pes tortus	Speecah delay, severe hearing loss, severe hypotonia, severe hyporeactivity	Normal

well as the periventricular, lobar, and subcortical white matter, which appeared hyperintense on T2-weighted images. T2-weighted and FLAIR images showed a curvilinear hyperintense streak between hypointense medial and lateral segments of both globi pallidi. A mild cerebral atrophy, and a thin corpus callosum were also observed.

Discussion

Fucosidosis is a rare lysosomal storage disorder characterized by the accumulation of different fucose-containing products in several organs, including the brain.

To date, few CT scans and MR images of the brain of patients with fucosidosis have been reported (5–9). CT features include hypodensity of the corona radiata, nuclei pallidi, and internal medullary laminae of the thalami (5, 6, 10). MR images show extensive and progressive changes in the signal intensity of the white matter, including the corpus medullare; the periventricular, lobar, and subcortical sovratentorial areas; internal and external capsules; and the internal medullary laminae of the thalami, which show hyperintensity on long-TR sequences (5–7, 9). The globi pallidi and substantia nigra may show high signal intensity on T1-weighted images and low signal intensity on T2-weighted and FLAIR images (5, 6, 9). Cerebral and cerebellar atrophy have been described in older patients, usually with fucosidosis type II (5, 6, 9–11).

The prominent white matter abnormalities observed in fucosidosis have been variably described as deficient myelination or severe demyelination; however, the extensive, symmetrical, and confluent white matter signal alteration are striking features of inherited myelin disorders and toxic encephalopathies, and much less so of acquired demyelinating disorders (4, 12). Neuropathologic analysis shows diffuse neuronal loss and ballooning: these changes are seen everywhere in the cerebral gray matter, but look more severe in the thalamus, hypothalamus, cerebral cortex, Purkinje cells, and nucleus dentatus. Severe loss of myelin associated with gliosis is appreciable. In the brain, there is a major accumulation of oligosaccharides rather than glycolipids that predominate as storage material in the liver. The brain may be large or small, depending on the stage of the disease (1–4).

The cause of MR signal alteration of the globus pallidus is not known with certainty. At 6 months of age, the globus pallidus and putamen begin to appear isointense to one another and hypointense with respect to the internal capsule on T2-weighted images. As the cerebral white matter myelinates, the basal ganglia become hyperintense with respect to the normal white matter of the brain. The globus pallidus usually changes to isointense with white matter before the age of 10 years, and becomes of lower signal than surrounding brain by the age of 15 to 20 years (12). The reported alteration of MR signal intensity in fucosidosis type I, ie, variable high signal intensity on T1-weighted images and low signal intensity on T2-weighted images (such as in our three patients), may suggest calcification or iron attributable to subacute hemorrhage. However, calcification has not been identified on CT scans performed at the same time of MR imaging (5, 6), and bilateral symmetrical microhemorrhage is unlikely (6). Another well-known possible explanation of high signal intensity on T1-weighted MR images is the accumulation of paramagnetic substances, especially manganese, which may escape hepatic clearances because of a portal-systemic shunt caused by chronic liver dysfunction (13–15) or a deposit in the brain because of overloading by most parenteral nutrition regimens (15). However, manganese deposits usually result in normal T2-weighted MR images with no signal loss. Furthermore, only 25% of the patients with fucosidosis present with elevation of liver enzymes, which is usually mild, as in our patients (2).

Within the globi pallidi of patients with fucosidosis, neuropathologic reports showed large amounts of macrophages laden with triglycerides, neutral fats, and cholesterol esters (3) as well as intracellular inclusion bodies, possibly as result of glycolipid accumulation (2). However, the hypoin-
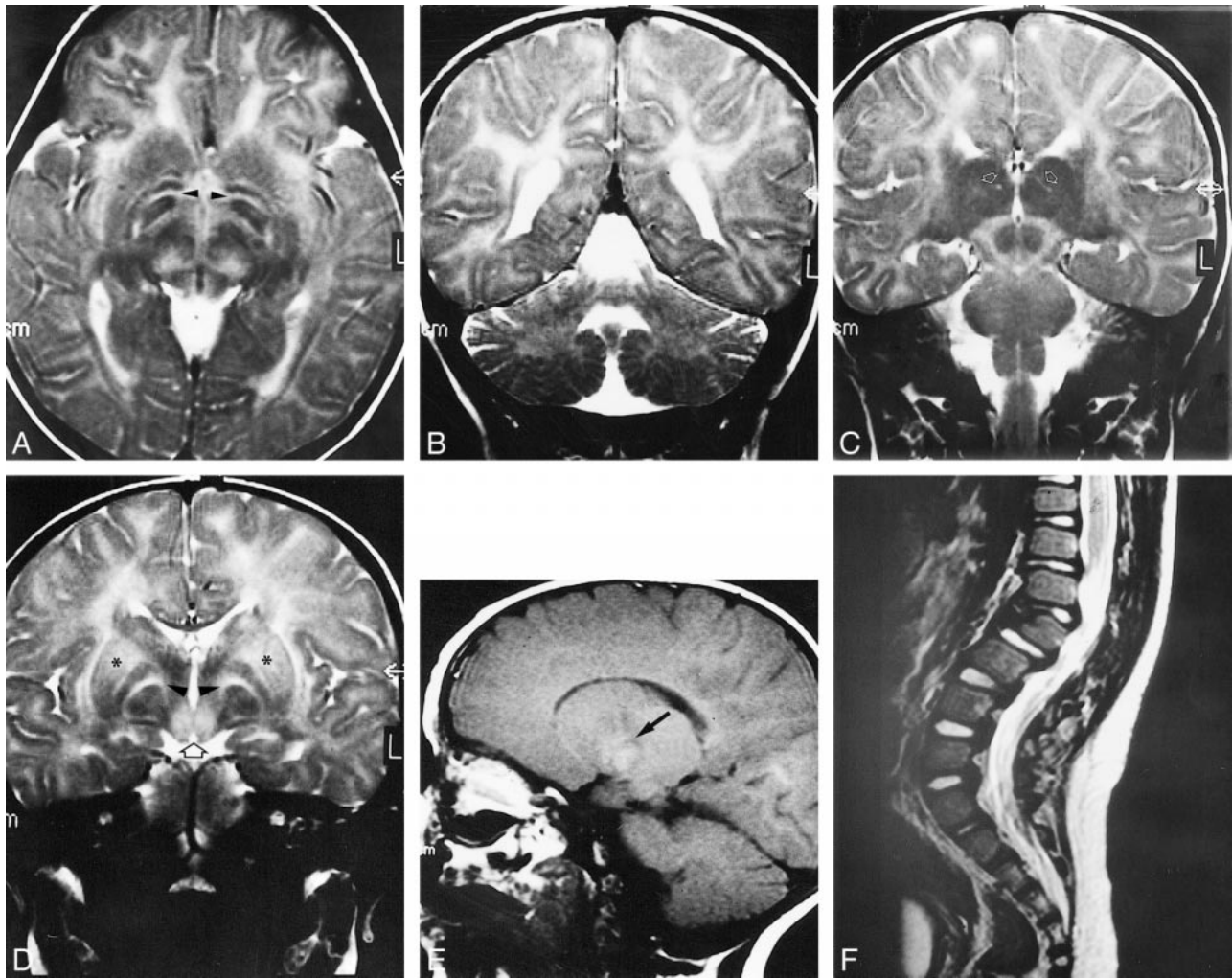
Fɪɢ 1. Patient 2, 2 1/2-year-old girl.

A, Turbo spin-echo (TSE) T2-weighted (TR/TE/excitations [2800/110/2]) axial MR image shows extensive high signal intensity of supratentorial white matter, as well as of the medial medullary laminae (*arrowheads*) between the medial and lateral pallidal segments, which appear hypointense.

B–D, Serial TSE T2-weighted (2800/110/2) coronal MR images confirm extensive signal intensity alteration of supratentorial white matter, and show altered signal in the corpus medullare. The internal medullary laminae of the thalami are hyperintense (*white open arrows*). A high signal intensity alteration is seen in both the putamina (*asterisks*) and hypothalamus (*black open arrows*). The abnormal signal intensity of the medial medullary laminae (*arrowheads*) splitting the medial from the lateral pallidal segment is better appreciated.

E, Spin-echo T1-weighted (550/15/2) sagittal MR image shows a hypointense streak (*arrow*) separating the two pallidal segments which appear hyperintense.

F, TSE T2-weighted (2736/150/4) sagittal MR image of the thoracolumbar spine shows anterior and posterior vertebral beaking.

tense signal on T2-weighted images have not been considered to be consistent with fat deposition (6). Acute damage or edema from oligosaccharide deposition has been considered a possible explanation for low-attenuation regions within the globi pallidi on CT scans (4–6); however, there are no available corresponding MR images.

In the patients reported herein, MR imaging showed some previously unreported findings. T2-weighted images showed hyperintensity of the putamina of patients 1 and 2, and diffuse hyperintense signal in the hypothalamus of patient 2. In all the patients, two curvilinear streaks of abnormal signal intensity were evident within the lentiform nucleus bilaterally: one was medial, within the globus pallidus, and the other lateral, between the globus pal-

lidus and the putamen. These streaks are consistent with medial and lateral medullary laminae of the globus pallidus, which are layers of vertical, ascending myelinated fibers dividing, respectively, the globus pallidus into a smaller medial (medial pallidal segment) with a larger, lateral part (lateral pallidal segment) and a lateral pallidal segment from the medial aspect of the putamen. The globus pallidus is encapsulated and traversed by numerous, coarse, heavily myelinated fibers, including afferent connections and a pallidofugal system. The signal alteration in the medullary laminae of the globus pallidus is strikingly similar to the subtle hyperintensity within the internal medullary lamina of the thalamus (5), which was present in all our patients. The internal medullary lamina of the thal-

amus is a thin, curved sheet of myelinated fibers, which splits anterosuperiorly in a Y-shaped manner, and divides most of the thalamus into medial and lateral groups of nuclei (16).

To the best of our knowledge, the combination of hypointensity of the globus pallidus and hyperintensity in its laminae on T2-weighted MR images has not been reported in other neurometabolic disorders. However, the review of the published MR images of a 19-month-old patient with infantile type O GM_2 gangliosidosis (Sandhoff disease), wherein basal ganglia were reported as normal, clearly showed both diffuse extensive white matter changes, and signal alteration in the globi pallidi (17). These findings were very similar to those shown in our three patients with fucosidosis type I. Thus, the MR features reported herein are not specific for fucosidosis type I, but are probably the results of an extensive white matter involvement, as well as the pallidal accumulation of glycolipids. Extensive white matter involvement may also contribute to the diffuse MR signal alteration that we have found in the putamen of patients 1 and 2, and the hypothalamus of patient 2. The putamen is permeated by delicate bundles of either finely myelinated or nonmyelinated, small-diameter fibers, including afferent connections and striatofugal fibers. The hypothalamus is a complex region permeated by a series of white matter tracts and nuclei, interconnections and more diffuse fiber arrays entering, leaving, passing through, or intrinsic to the region (16). Specific involvement of the putamen and hypothalamic white matter bundles may justify the lack of symptoms from direct putaminal and/or hypothalamic gray matter involvement, such as obsessive compulsive traits, dysphonia, neglect, aggressivity, anorexia, hyperphagia, polydipsia, gelastic seizures, or thermal dysregulation.

A mild cerebral atrophy with thinning of the corpus callosum was evident only in our patient 3. This might be justified by a less advanced disease progression in patients 1 and 2, or a great variability of the phenotype of fucosidosis type 1.

Finally, to the best of our knowledge, we have presented the first MR image of the thoracolumbar spine of a patient with fucosidosis. The disease usually results in skeletal maturation delay, and dysostoses multiplex may develop, mainly affecting the spine, pelvis, hips, as well as the long bone diaphyses. The lower thoracic and lumbar vertebrae may be flattened and beaked, as occurred in our patient 2.

In conclusion, the MR findings reported herein expand the neuroradiologic spectrum of fucosidosis type I. The extensive involvement of a combination of cerebral white matter, including the deep layers crossing the thalamus, lentiform nucleus, and hypothalamus, and the corpus medullare, as well as the low signal of the globus pallidus, may differentiate it from other neurometabolic disorders. However, a complete understanding of the significance of changes documented by neuroimaging still requires further serial studies as well as neuropathologic and biochemical studies on cerebral tissue.

Acknowledgments

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