

## Neuropathology Education

# An 11-year-old boy showing rapid psychomotor regression and diffuse cerebral white matter lesions

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## CLINICAL HISTORY

A male patient was born at term to healthy parents with normal delivery after an uneventful pregnancy. There was no family history of neuromuscular disorders. His development was normal in early infancy: he showed social smiling at 5 months of age, recognition of his mother at 6 months and head control at 7 months. However, he could neither roll over nor utter meaningful words. He developed mild psychomotor developmental delay and myoclonic seizures in his legs around the age of 12 months. Clinical examination showed frontal bossing (head circumference, 48 cm), scoliosis, hepatosplenomegaly, poor head control, visual disturbance, bulbar palsy, hypotonia and brisk deep tendon reflex. He was admitted to our center at the age of 19 months. He lost voluntary eye tracking and reactions to environmental stimuli, and required tube feeding to avoid aspiration pneumonia. He developed severe motor disabilities and became bedridden. The lesions of the bilateral thalamus were hypodense on CT scan and T2-hyperintense on MRI, as reported previously.<sup>1</sup> The cerebral white matter gradually showed T1 low and T2 high-signal changes on MRI (Fig. 1A). Since he had recurrent episodes of aspiration pneumonia and suffered from subsequent cardiopulmonary arrest, he received continuous mechanical ventilation after the age of 4 years. Recurrent urinary tract infection occurred and he died of acute renal failure at the age of 11 years.

## GENERAL PATHOLOGY

Light microscopy showed infiltration of histiocytes, positively stained with PAS, in the liver, spleen and lung.

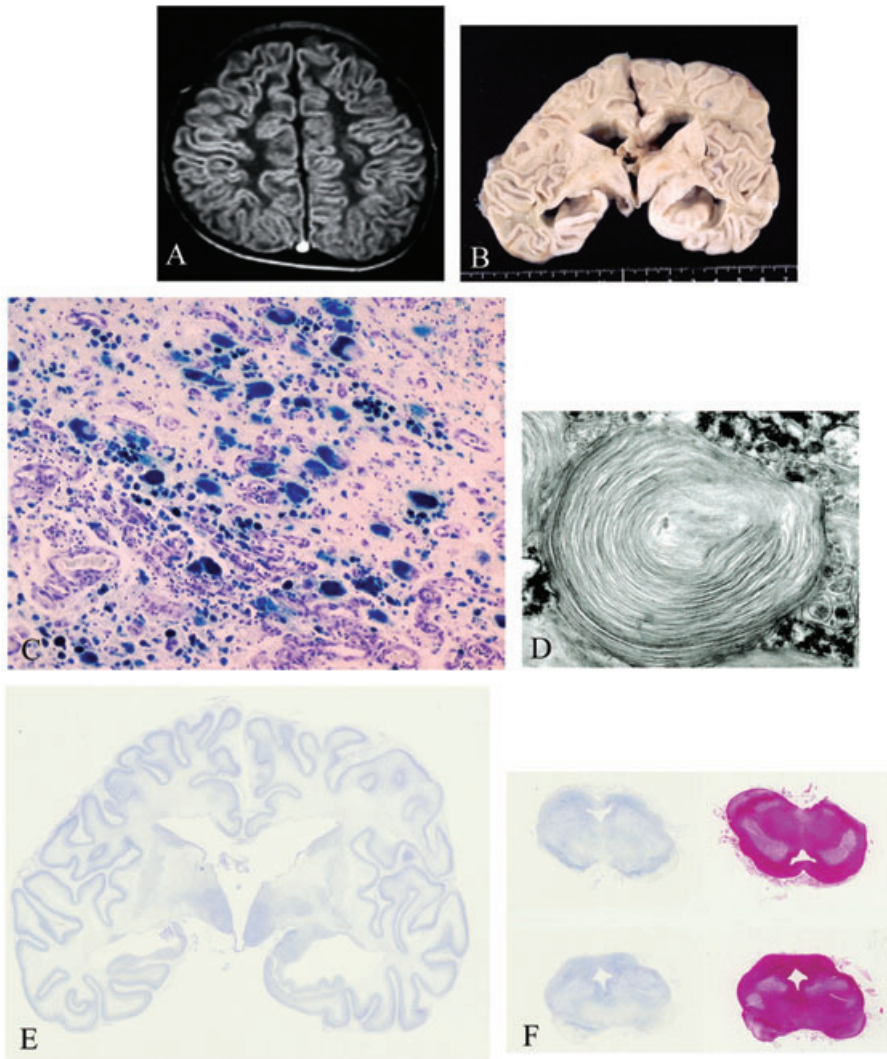
Accumulation of PAS-positive substrates was found in the neurons of the Auerbach and Meissner plexus. The liver weighed 431 g, showed fatty metamorphosis, and bridging fibrosis with cell infiltration in the Glisson's capsule. The lung showed interstitial fibrosis. In the kidney, the glomerular epithelial cells were swollen and filled with vacuoles.

## NEUROPATHOLOGY

The brain weighed 897 g at autopsy. Macroscopically, the pia mater showed remarkable thickening throughout the brain. The cerebrum, cerebellum and brainstem were slightly small. Cross-sections showed that the cerebral cortex was unusually thin, and there was a reduction in volume and gelatinous softening of the white matter. The bilateral lateral ventricles and the third ventricle were moderately enlarged (Fig. 1B). The atrophic basal ganglia and thalamus had dark brown and white discoloration, respectively. Severe atrophy and softening of the white matter was observed in the cerebellum. In the brain stem there was bilateral necrosis in the mesencephalic and pontine tegmentum in addition to the substantia nigra. The cerebral peduncle, longitudinal fasciculus of the pons and the medullary pyramis were atrophic.

On microscopic examination, the meninx showed fibrous thickening, but there was no leukocyte infiltration in the subarachnoid or Virchow-Robin spaces. Severe neuronal loss with gliosis was observed in the cerebral and cerebellar cortex, basal ganglia, thalamus and pontine nucleus, while neurons were mildly reduced in the hypothalamus, cerebellar dentate nucleus, locus ceruleus and raphe nuclei of the pons. The neurons in the spinal cord were comparatively preserved. The remaining neurons showed swelling with intracytoplasmic accumulation of materials, which were weakly PAS-positive and strongly

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**Fig. 1** (A) T1-weighted MRI image taken at the age of 2 years and 10 months shows low-signal changes that are diffuse in the cerebral white matter. (B) Cross-section shows thinning of the cerebral cortex, as well as severe reduction in volume and softening of the cerebral white matter. (C) Remaining neurons in the locus ceruleus shows accumulation of materials strongly stained with luxol fast blue (LFB) by KB stain. (D) Electron microscopy showing membranous cytoplasmic bodies. (E) The cerebral white matter was sparse and did not stain strongly for LFB. (F) The upper and lower midbrain shows symmetrical necrosis in the tegmentum and substantia nigra. KB and HE stains.

stained for luxol-fast blue with KB stain (Fig. 1C). On electron microscope examination, the cytoplasm of neurons were filled with concentrically arranged, membranous cytoplasmic inclusion bodies (Fig. 1D). Severe loss of the myelinated fibers was observed throughout the white matter of the cerebrum (Fig. 1E), cerebellum, brainstem and spinal cord, except for the posterior funiculus of the spinal cord. Severely affected regions of the cerebrum showed sparsity of white matter, whereas mildly affected regions had fibrillary gliosis. Bilateral brainstem tegmentum and substantia nigra showed necrosis, neovascularization and cellular infiltration (Fig. 1F). The meninges of the cerebrum, cerebellum and brainstem were severely thickened and accompanied with mild cellular infiltration.

## DIAGNOSIS

Infantile GM1 gangliosidosis.

## DISCUSSION

Infantile GM1 gangliosidosis is a rare autosomal-recessive lysosomal storage disorder caused by a deficiency of lysosomal  $\beta$ -galactosidase, which results in neural and visceral accumulation of GM1 gangliosides.<sup>1</sup> On the bases of onset age and clinical course, GM1 gangliosidosis is classified into infantile, late infantile/juvenile and adult form. Infantile GM1 gangliosidosis is the severest form characterized by onset in early infancy, failure to thrive, facial dysmorphism, skeletal abnormalities, hepatosplenomegaly, macular cherry-red spots, psychomotor developmental delay, and generalized hypotonia, which gradually develops to rigospasticity. Patients become bedridden during childhood and die in their first decade. This patient was diagnosed as having GM1 gangliosidosis at the age of 13 months, since macular cherry-red spots were noted during a fundoscopic examination and biochemical analysis of lysosomal enzymes in fibroblasts revealed a  $\beta$ -galactosidase deficiency.

During the early stages of disease, patients with infantile GM1 gangliosidosis have thalamic lesions that are hyperdense on CT scan and T2-hyperintense on MRI, which were also present in our case. The same finding is also seen in cases of infantile GM2 gangliosidosis and Krabbe's disease.<sup>1,2</sup> Nevertheless, the pathological substrate of these thalamic changes remains obscure. As the disease advances, neuroradiology reveals white matter changes and cortical atrophy,<sup>1,2</sup> findings that can be pathologically proven at autopsy.<sup>3-7</sup> It is thought that the white matter lesions may be caused by delayed or arrested myelination, oligodendrocyte dysfunction and/or axonal disturbances subsequent to the damage of cortical neurons. Relatively long survival may lead to the formation of diffuse and typical white matter changes, as in this case. Interestingly, the bilateral symmetrical necrosis of the brainstem tegmentum and substantia nigra in this patient partially mimics the changes observed in Leigh's syndrome, although these may have been caused by hypoxia following cardiopulmonary arrest.

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