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Short Communication

Natural history of motor neuron disease in adult onset GM2-gangliosidosis: A case report with 25 years of follow-up

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ABSTRACT

An adult with Sandhoff disease presented with pure lower motor neuron phenotype. Twenty years later, he showed signs of upper motor neuron involvement. 25 years from the onset, his muscle weakness slightly worsened but he was fully independent in activities of daily living.

GM2-gangliosidosis can manifest as a motor neuron disease with a slowly progressive course. The correct knowledge of the natural history can be really important to achieve the diagnosis, design new therapies and evaluate clinical trials.

1. Introduction

Sandhoff disease is a glycosphingolipid storage disorder caused by a defect in ganglioside metabolism due to mutations in the *HEXB* gene that disrupt the function of the *N*-acetyl-beta-D-glucosaminidase isoforms Hex A and Hex B [1]. Ganglioside GM2 accumulates in the neural cells of affected individuals, leading to swollen neurons with massive accumulation of storage material appearing as membranous cytoplasmic bodies throughout the central and peripheral nervous system [2].

Depending on the residual Hex activity, acute infantile, subacute juvenile, and chronic adult-onset forms of GM2-gangliosidosis can occur. Usually, early-onset Sandhoff disease presents before 9 months of age with progressive psychomotor retardation and early death, while later onset forms are relatively less severe. Slowly progressive neurological symptoms are predominant both in subacute and chronic

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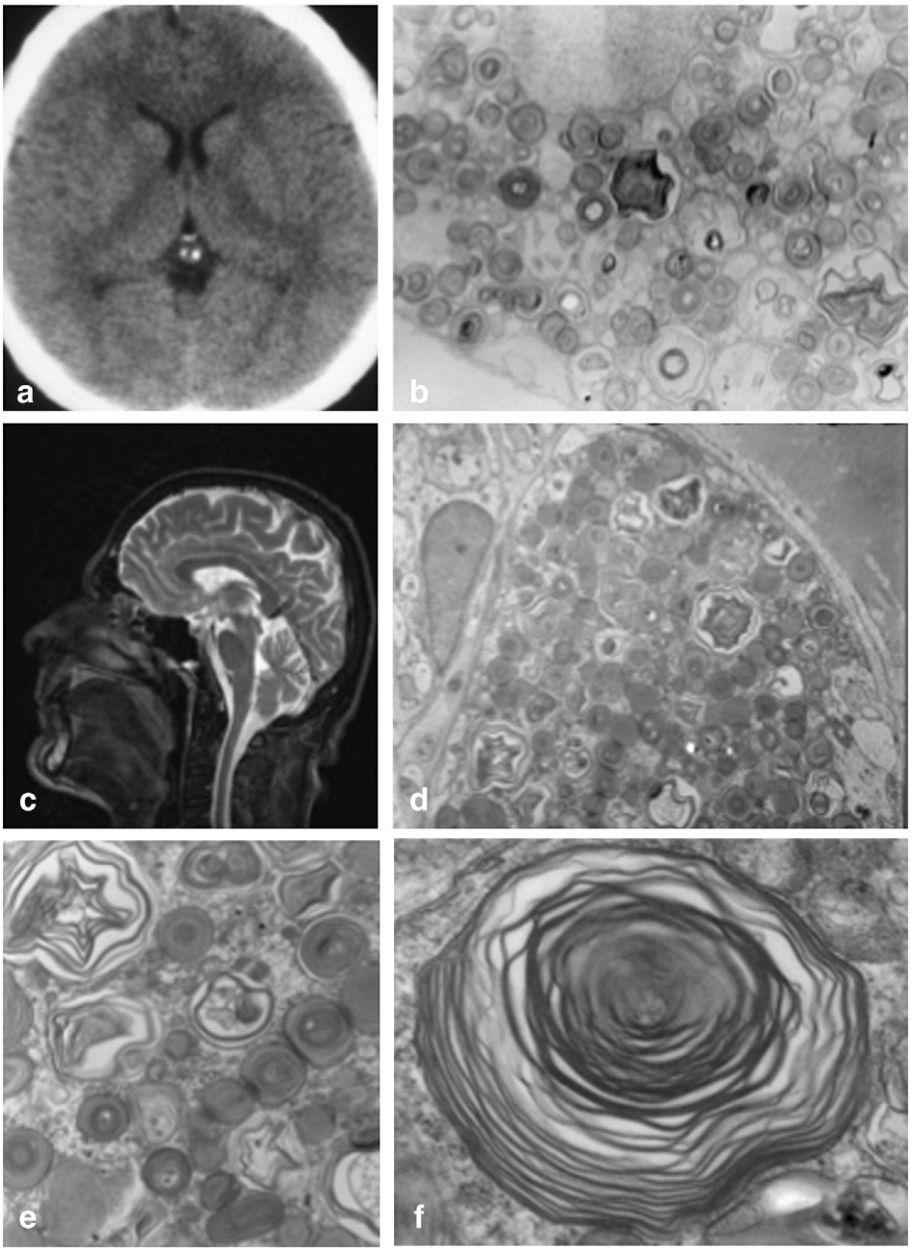

Fig. 1. a: Brain TC scan performed when patient was 28 years old. Section at level of deep gray matter didn't show the bilateral symmetric thalamic altered signal typical of the infantile form. b: Electron microscopy of the rectal biopsy at diagnosis showed cytoplasmic membranous bodies in neurones of the myenteric plexus (3000× magnification). c: Sagittal T1-weighted brain MRI showing a mild cerebellar atrophy at 25th year of follow-up. d–f: Rectal biopsy 25 years after the diagnosis. At ultrastructural level, neuronal inclusions were pleiomorphic, composed of single or multiple layers of concentric outer membranes surrounding inner components of short, straight or curved membranes as well as membranous cytoplasmic bodies (3000×, 7000× and 30,000 X magnification, respectively).

GM2-gangliosidosis. They usually affect spinocerebellar, autonomic and motor neuron functions, in variable association with psychiatric and cognitive symptoms, and eventually leads to severe disability [3,4].

Since the unique phenotype of motor neuron disorder in adult Sandhoff diseases was first recognized, an increasing number of cases have been reported. Many of them were characterized as progressive spinal muscular atrophy due to predominant lower motor neuron abnormalities [2,5], whereas an increasing number of cases showed amyotrophic lateral sclerosis-like phenotype due to the involvement of upper motor neurons [6,7].

Although the natural history of the infantile and juvenile forms of GM2-gangliosidosis has been properly characterized, the disease course of late-onset form, and in particular of patients with motor neuron phenotype, is not well defined [8,9].

We described here the 25-year follow-up of an adult patient with GM2-gangliosidosis, thus detailing the natural history of the late-onset form of this disease.

2. Case report

The initial history of the patient reported here has been previously described [10]. Briefly, he is a 53 year-old man who presented, at the age of 28, when he was a rock climber, with progressive difficulty in climbing and going down mountain paths and getting up from supine position. Neurological examination showed mild proximal lower limb muscle weakness (4 MRC), slight bilateral wasting of hypothenar and thigh muscles, widespread spontaneous fasciculations in both arms and legs and brisk tendon reflexes with downgoing plantar responses; neither signs of cerebellar, sensory or autonomic dysfunction, nor cognitive impairment were observed.

Electromyography demonstrated signs of denervation in lower limbs, whereas nerve conduction study and brain CT scan were normal (Fig. 1a). Biochemical studies, using the artificial fluorogenic substrate 4-methyl-umbelliferyl-2-deoxy-2-acetamido-b-D-glucopyranoside [2], documented a strongly reduced total Hex activity in leukocytes (13% of normal). Hex A activity with substrate 4-methyl-umbelliferyl-beta-D-N-acetylglucosaminide-sulfate was 108 nmol/mg/h (normal value > 210; range 210–1241). On rectal biopsy, the presence of storage material represented by membranous cytoplasmic bodies was detected in neurons of the myenteric plexus (Fig. 1b). *HEXB* genetic analysis revealed a compound: Δ5′ deletion and c.C1214T (p.Pro417Leu) missense mutation [10].

Twenty years later, when he was 48, bilateral Babinski sign appeared and neurophysiological study showed a subclinical peripheral sensory neuropathy in lower limbs. When he was 52, treatment with the *N*-alkylated imino sugar miglustat was started. Twenty-five years from the onset, his muscle weakness in lower limbs slightly worsened (3 MRC) and mild weakness appeared in both arms (4 MRC). Sensory, cerebellar and autonomic functions were spared and brain magnetic resonance imaging (MRI) showed only mild cerebellar atrophy (Fig. 1c). A new rectal biopsy showed the identical presence of storage material in autonomic neurons (Fig. 1d–f). He was fully independent in activities of daily living.

3. Discussion

The residual enzyme activity and the type of mutations harbored by our patient are compatible with a late-onset phenotype [10]; even if ataxia and dysarthria are common presenting symptoms and psychiatric disturbances are also often seen in late-onset Sandhoff disease, he showed only a clinically pure motor neuron disorder with a subclinical sensory involvement and a very slowly progressive course. The same genomic condition (a genetic compound of a missense mutation and a null mutation) harbored by our patient were reported two other adult patients with Sandhoff disease and a severe impairment of the autonomic nervous system from the onset, indicating that the patient's genotype may not result in an accurate prediction of the ultimate phenotype [10,11]. Although we cannot exclude a positive impact of the treatment on the clinical course of our patient, we postulate a possible individual susceptibility to the involvement of different neuronal systems and the role of unknown genetic (i.e. polymorphic variants) and epigenetic factors to modulate the disease phenotype [12]. Of extreme interest, in our patient the second rectal biopsy demonstrated that swollen neurons were still present and functioning (as demonstrated by the lack of autonomic dysfunction) 25 years later. This suggests that residual Hex

activity present in this patient is just below the critical threshold of normal levels needed to prevent the accumulation of GM2 ganglioside. At the same time, the Hex activity has been enough to preserve over a long period a physiological activity, at least in a specific cell sub-type (i.e. autonomic neurons), also in the presence of storage material [13].

The lack of data on the course in large Sandhoff disease populations underlines the importance of collecting informations regarding the natural history of this rare condition. As research aimed to treatment strategies is emerging [14,15], the knowledge of phenotypes is a very important requirement for the development of clinical trials and for predicting the clinical course of this debilitating condition in individual patients.

In conclusion, to our knowledge, this is the longest follow-up in a patient with Sandhoff disease leading to a motor neuron phenotype and underlines how a clinical history of motor neuron disorder, in adult GM2-gangliosidosis, may have a slowly progressive course. The evaluation of β-hexosaminidase activity should be considered for children and young adults with any form of motor neuron disease.

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The authors declare no conflicts of interest.

All co-authors have read and agreed the contents of the paper.

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