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Short Communication

Abnormal glycogen in astrocytes is sufficient to cause adult polyglucosan body disease

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ABSTRACT

Background: A 45-year old woman of Cambodian ethnic background presented with fatal respiratory failure due to a severe diaphragmatic dysfunction. Two years before, she had developed early onset of urinary symptoms.

Methods and results: Neuroimaging showed atrophy of the spine and medulla as well as a leukodystrophy affecting both supra- and infra-tentorial regions. At autopsy, polyglucosan bodies (PB) were seen in several peripheral tissues, including the diaphragm, and nervous tissues such as peripheral nerves, cerebral white matter, basal ganglia, hippocampus, brainstem and cerebellum. Immunohistochemistry and electron microscopy of the brain revealed an exclusive astrocytic localization of the PB. The diagnosis of adult polyglucosan body disease (APBD) was confirmed by enzymatic and molecular studies.

Conclusion: Storage of abnormal glycogen in astrocytes is sufficient to cause the leukodystrophy of APBD. Since brain glycogen is almost exclusively metabolized in astrocytes, this observation sheds light on the pathophysiology of APBD. In addition, this is the first report of an APBD patient presenting with a subacute diaphragmatic failure.

1. Introduction

Adult polyglucosan body disease (APBD) is a rare progressive neurological disorder due to a deficiency in glycogen branching enzyme (GBE) (Bruno et al., 1993; Moses and Parvari, 2002). Polyglucosan bodies (PB) refer to the accumulation of glucose polymers, staining strongly with periodic acid Schiff (PAS), due to the abnormal synthesis and degradation of glycogen. Glycogen storage type IV (GSD IV) was first described in neonates and children as Andersen disease. In the adult-onset form (APBD), the symptoms begin in the fourth to sixth decade. The most frequent inaugural symptom is bladder dysfunction, often followed by motor and sensory deficits, and mild cognitive impairment in about half of the patients. APBD is characterized by a leukodystrophy on brain MRI and a severe atrophy of the spine and medulla (Lossos et al., 1998). APBD is autosomal recessive, affecting predominantly Ashkenazi Jewish families (Moses and Parvari, 2002).

We report detailed neuropathological analyses of an APBD case with unusual clinical presentation. This study enlarges the phenotypic spectrum of GSD IV and contributes to expand our understanding of brain glycogen metabolism.

2. Patient and methods

A 45 year-old Cambodian woman was admitted in the emergency room because of subacute respiratory failure. Family history was uninformative and there was no consanguinity. Over the preceding 5 years, the patient had been treated for breast cancer. On admission,

Abbreviations: PB, polyglucosan body; PAS, periodic acid Schiff; APBD, adult polyglucosan body disease; GBE, glycogen branching enzyme; GSD, glycogen storage disease; NF, neurofilaments; LFB, Luxol-fast blue; GFAP, glial fibrillary acidic protein; AQP4, aquaporin 4; MBP, myelin basic protein.

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the patient required an emergency tracheal intubation because of hypercapnic coma. The first line of investigations did not reveal any sign of infection or inflammation, neither pulmonary embolism. Proximal four-limb weakness was noticed with hyperreflexia, suggesting a motor neuron disease. Nevertheless, the electromyography performed at bedside was normal, as well as standard biochemical analyses in blood and cerebrospinal fluid. Full-body CT scan displayed metastases in the liver and in the spinal column.

On further inquiry, family members reported bladder dysfunction, which started about 2 years earlier, and mild difficulty walking over the past months. In addition, the family indicated that the patient had suffered from dyspnea for a couple of weeks. The clinical status of the patient worsened as she developed a pulmonary infection. Within a few days, she suffered from a severe acute respiratory syndrome and died 3 weeks following admission.

The study was approved by local ethics committees and written informed consent for autopsy was obtained from the patient's relatives. In the brain, the following regions were analyzed: midfrontal gyrus, superior temporal gyrus, caudate nucleus, thalamus and mamillary bodies, hippocampus, calcarin sulcus, cerebellum, substantia nigra, motor cortex, lenticular nucleus, pons, medulla oblongata, spinal cord, orbital–frontal cortex and temporal amygdala. Details on the antibodies that were used for immunohistochemistry are listed in the Supplementary table. In order to confirm the cellular localization of PB, the immunolabelling of neurofilaments (NF) was followed by PAS stain. On muscular and neural sections PAS technique, Masson's Trichromic stain, Congo Red and Luxol-fast blue (LFB) staining were performed. Specimens of sural nerve and musculocutaneous nerve were analyzed by transmission electron microscopy.

The enzymatic activity of GBE was assayed in the patient's leukocytes obtained prior to death using an indirect method (Brown and Brown, 1966). Genomic DNA was extracted from peripheral blood leukocytes using standard procedures. The 16 exons and exon/intron boundaries of the *GBE1* gene were amplified and PCR products were sequenced using the Big-Dye terminator v3.1 cycle sequencing kit (Applied Biosystems, Foster City, CA, USA) and an ABI Prism 3730 Genetic Analyzer (Applied Biosystems).

3. Results

Neuroimaging on a 3 T scan displayed noteworthy atrophy of the medulla and of the spinal cord (Fig. 1A). Brain MRI also revealed a diffuse white matter disease (Fig. 1B). Hyperintense white matter abnormalities on T2 and FLAIR sequences were present in the medulla and pons, in the pyramidal tracts and the medial lemniscus (Fig. 1B). In the cerebral hemispheres, white matter lesions were symmetric and confluent, affecting the frontal, parietal, temporal and occipital areas. The external capsule and the posterior limb of the internal capsule were also affected while the anterior limb was spared (Fig. 1B). The abnormal white matter areas had normal or hypointense signal on T1-weighted images (data not shown). In addition, there was diffuse cortical and subcortical atrophy, mild vermian atrophy and thin corpus callosum (data not shown). None of the white matter lesion showed contrast enhancement. This pattern suggested APBD due to GBE deficiency.

At autopsy, numerous PB were observed in the myoepithelial cells of the sweat glands, the cardiac and diaphragmatic myocytes, and in the sural nerve (Supplementary Figs. 1A, B, C and D). Of note, PB were relatively more abundant in the diaphragm than in limb muscles. In the sural nerve, PB appeared surrounded by LFB, compatible with their localization in Schwann cells rather than in axons (Supplementary Fig. 2), but were not found in serial semi-thin sections. Externally, the cerebrum and brainstem were normal. By contrast, the spinal cord was severely and globally atrophic (Supplementary Fig. 3). Examination of the brain sections showed atrophy of the corpus callosum associated with grayish discoloration of the white matter with sparing of

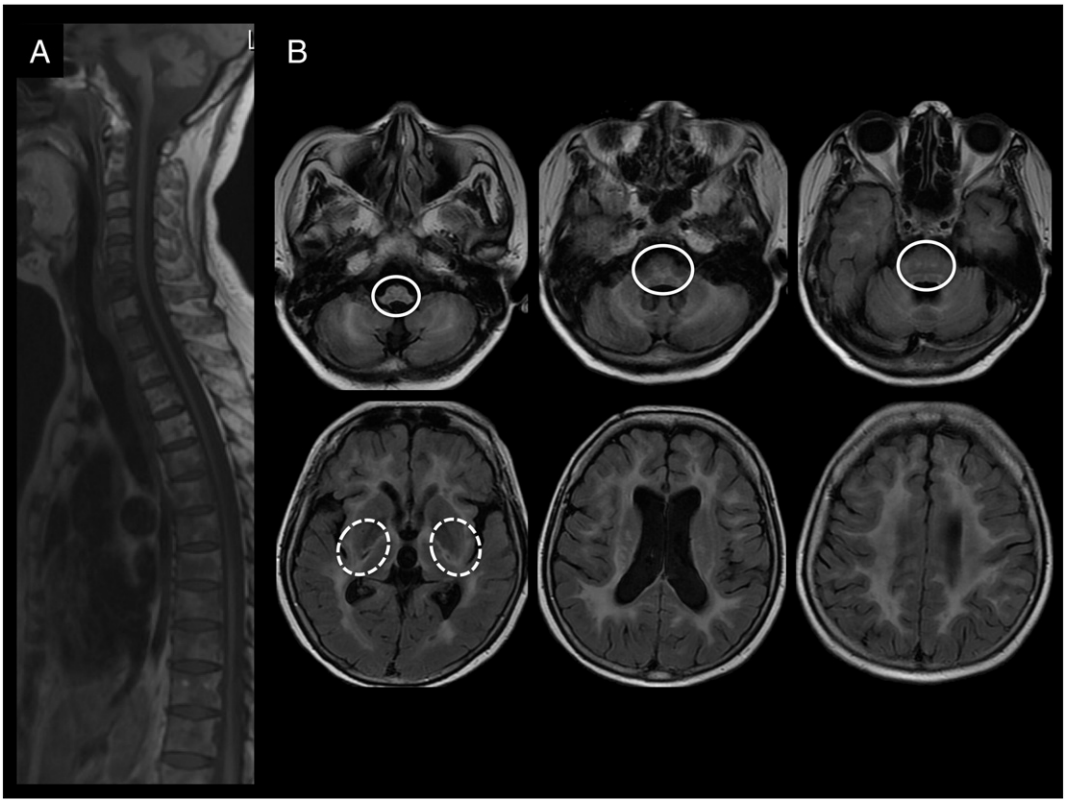

Fig. 1. Brain and spinal MRI. A) T1 sagittal scan showing important medulla and spinal cord atrophy. B) FLAIR axial scans showing hyperintense white matter changes in the periventricular regions, the external capsule and the posterior limb of the internal capsule (dashed circles), the cerebellar hemispheres and in the pyramidal tracts and medial lemniscus of the medulla and pons (solid circles).