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A Case Of Adult Polyglucosan Body Disease With Chronic Inflammatory Demyelinating Polyneuropathy Like Presentation

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Abstract
Introduction: *Adult polyglucosan body disease (APBD) is an autosomal recessive leukodystrophy caused by abnormal intracellular accumulation of glycogen byproducts. This disorder is linked to a deficiency in glycogen branching enzyme-1 (GBE-1). Neurologic manifestations include upper and lower motor neuron signs, dementia, and peripheral neuropathy. APBD is typically a progressive disease. In this report, we discuss a novel case of APBD in a patient who had flaccid pararperesis.*
Case report: *We describe a elderly woman with an unusual phenotype manifesting as progressive lumbosacral plexopathies, without central sensory and corticospinal tract involvement. Magnetic resonance imaging of the brain and spine was normal. Nerve conduction study suggestive of sensory motor axonal neuropathy. On nerve biopsy, large polyglucosan bodies were noted in the endoneurium. The patient was found to be compound heterozygous for 2 novel mutations in GBE1.*
Conclusions: *APBD is a rare disorder that can affect the nervous system. The diagnosis can be confirmed with a combination of genetic testing and pathologic analysis.*
Keywords: *Adult polyglucosan body disease, Chronic inflammatory demyelinating polyneuropathy, Glycogen storage diseases, Glycogen branching enzyme.*

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I. Introduction

Glycogen is essential for energy supply and glucose homeostasis. Pathologic accumulation of glycogen in tissue is associated with a group of disorders known as glycogen storage diseases (GSD). Glycogen branching enzyme (GBE) deficiency, also known as GSD-IV, is a rare genetic disorder. The frequency of all glycogen storage diseases is 1:10,000, with GBE deficiency constituting approximately 3% [1]. Adult polyglucosan body disease (APBD) is associated with progressive central (CNS) and/or peripheral nervous system (PNS) involvement [2].

APBD, is a rare autosomal recessive disorder that has been diagnosed in patients with age more than 40 years [3]. There is no known gender predisposition [9]. APBD classically presents as a combination of peripheral neuropathy (80%), cortical/subcortical dementia (64%), neurogenic bladder (72%), and upper and lower motor neuron signs (80%) [4]. Rare symptoms include severe orthostatic vomiting, transient neurologic deterioration, unilateral progressive plexopathy, extrapyramidal syndrome, and severe cardiomyopathy, often leading to misdiagnosis. As a consequence, affected individuals may be subjected to ineffective treatment with disease-modifying agents, immunosuppressive therapy, antiplatelet agents or surgical procedures such as decompression surgery for presumed spine degenerative disease with no clinical benefit [5]. The clinical course of APBD is typically progressive, with the majority of patients receiving only supportive care. In this case report, we present a 50-year-old woman who presented with neurologic symptoms mimicking chronic inflammatory demyelinating polyneuropathy (CIDP), with workup ultimately revealing pathological findings pathognomonic of APBD.

II. Case report

A 50 year old woman presented with insidious onset progressive weakness of both lower limbs with proximal weakness in the form of difficulty to get up from squatting, difficulty to climb upstairs and difficulty in gripping slippers which was associated with thinning of the lower-limbs with no sensory and autonomic symptom.

The patient had no significant past medical history. Birth and developmental milestones history was unrevealing. There was no reported family history of any inherited neuromuscular or degenerative neurologic

disorders. The patient had no known history of alcohol consumption, smoking or illicit drug use. Further history revealed a progressive course of gait difficulty over the past few years requiring the use of a walker or cane. The patient felt these changes were likely age-related and continued to work full-time without seeking any medical evaluation.

General examination was notable for skin abrasions on the left shin area, supporting the history of trauma related to fall. The patient was conscious and coherent. Cranial nerve examination was normal. Motor examination revealed no wasting with hypotonia in both lower limbs at knee and ankle joints with absent deep tendon reflexes. Examination of different sensory modalities was normal.

Laboratory work-up included a complete blood count which revealed a white blood cell count of 8 thousand/cmm (normal range: 4.5–11 thousand/cmm), red blood cell count of 4 million/cmm (normal range: 4.7–6.1 million/cmm), platelet count of 230 thousand/cmm (normal range: 150–350 thousand/cmm), hemoglobin of 12.3 g/dL (normal range: 12–17 g/dL), and hematocrit of 38% (normal range: 38–48%). Comprehensive metabolic panel revealed a random blood glucose level of 110 mg/dL (normal range: 99–140 mg/dL), blood urea nitrogen of 19 mg/dL (normal range: 7–20 mg/dL), serum creatinine of 0.8 mg/dL (normal range: 0.7–1.3 mg/dL), sodium of 138 mmol/L (normal range: 135–145 mmol/L), and potassium of 4.5 mmol/L (normal range: 3.5–5.5 mmol/L). Further work-up revealed a HbA1c of 5.5% (normal is less than 5.7%), thyroid stimulating hormone of 1.5 uIU/mL (normal range: 0.4–4.0 uIU/mL), low-density lipoprotein of 90 mg/dL (optimal level is less than 100 mg/dL), and total serum cholesterol of 140 mg/dL (optimal level is less than 200 mg/dL). Serum lactate, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, and glutamic acid decarboxylase antibody were within normal limits. Computed tomography (CT) of head without contrast revealed normal. CT angiography of the head and neck showed no evidence of vasculopathy in the anterior or posterior circulation. Magnetic resonance imaging (MRI) of the brain and cervical spine revealed normal [figure-1].

Further workup included a lumbar puncture, with cerebrospinal fluid (CSF) analysis revealing a glucose level of 78 mg/dL (normal range: 50–80 mg/dL), protein of 40 mg/dL (normal range 15–60 mg/dL), white blood cell count of 2/cmm (normal range 0–5/cmm), and no red blood cells. CSF cultures revealed no growth of any organisms and complete meningitis/encephalitis panel was unremarkable. Nerve conduction study suggestive of axonal sensorimotor polyneuropathy. Sural nerve biopsy revealed intra-axonal basophilic inclusions (polyglucosan bodies) [figure-2]. On electron microscopic examination, the inclusions were located mainly within myelinated nerve fibers and consisted of branched filaments that were 6 to 8 nm wide. The genetic testing exome sequencing was performed two novel heterozygous missense variants of the GBE-1 gene which are transferred via an autosomal recessive mode of inheritance, c.691 + 2 T > G and c.1544 + G > A. Genetic testing for mitochondrial disorders was unremarkable.

III. Discussion

Glycogen is the storage form of glucose in cells and is essential for energy supply and homeostasis. Each glycogen granule consists of a highly branched polymer of glucose molecules connected by α-1,4-glucosidic linkages, and branched by α- 1,6-glucosidic linkages, making it soluble and available as an energy source. Any abnormality in the branching structure of glycogen may potentially compromise its function, leading to its storage as a polysaccharide known as polyglucosan (PG), which has fewer branched points, more numerous α-1,4-linked units, and longer peripheral chains. PG is an insoluble molecule that can precipitate into PG bodies (PGBs), deposits which do not degrade into free glucose to meet physiologic demands of energy supply [2].

APBD is a clinicopathologic entity that has been rarely described with a prevalence of less than 1 in a million. Affected individuals typically exhibit a progressive dysfunction of the CNS and/or PNS over the course of several years, with the diagnosis typically made after 4th decade of life. The GBE-1 gene encodes the enzyme GBE, which catalyzes the last step in the biosynthesis of glycogen, adding α- 1,6-branches to the developing molecule. Dysfunction or deficiency of GBE can lead to intracellular deposition of inclusion bodies that can disrupt cellular function within the nervous system [2]. PGBs are believed to be neurotoxic deposits that can trigger mechanical disruption of axons and pathological changes in the surrounding myelin structure [3,16]. Dysfunction in the ubiquitin-proteasomal system (UPS) and other autophagic processes have been implicated in many pathological conditions associated with PG storage [2].

The characteristic neuroimaging findings include diffuse, symmetric T2 white matter hyperintensities with predominance in the periventricular areas, temporal and occipital lobes, with involvement of the pyramidal tracts and medial lemniscus [6]. Other classic imaging features include medullary and cervical spinal cord atrophy, constituting the hallmark of APBD [6]. Atrophy of the cerebral hemispheres, cerebellar vermis, and thinning of the corpus callosum are less commonly seen.

Findings on electrodiagnostic studies are typical of an axonal sensorimotor polyneuropathy, although demyelinating features have also been described. Somatosensory evoked potential studies may show prolonged lumbar to cortical interpeak latencies [7]. The nonspecific imaging findings associated with APBD make the diagnosis a challenging one. A recent literature review reported several cases of APBD that were initially

diagnosed as alternative neurologic conditions such as multiple sclerosis, amyotrophic lateral sclerosis, CNS vasculitis, and cerebral small vessel ischemic disease, mainly due to the overlapping clinical and neuroimaging features [5].

APBD derives its name from the pathologic findings associated with this disorder. PGBs are defined as periodic acid-Schiff positive, diastase-resistant inclusion bodies that can be found intracellularly throughout the CNS and PNS. These findings are typically found after postmortem tissue analysis, but the diagnosis can also be made during the early stages of the disease by sural nerve biopsy. The results of the laboratory studies of our patient, including an axonal peripheral neuropathy, MRI findings and sural nerve biopsy findings are consistent with polyglucosan body disease. Although nerve biopsy can show accumulation of PGBs, clinical correlation and confirmatory genetic testing remains necessary for a definitive diagnosis as PGBs can accumulate at low levels in the nervous system during non-pathological aging [3].

Genetic testing on our patient revealed the presence of known heterozygous variants, including the c.691 + 2 T > G mutation, which have been previously associated with GBE-1 deficiency and development of APBD [8]. Abnormal polyglucosan deposition can also occur in the liver or kidneys, causing other systemic manifestations [3]. Early diagnosis of APBD may be essential for the design and efficacy of future therapeutic trials. Repletion of the defective lysosomal acid maltase has been proposed as a treatment for GSD-II, or Pompe disease. Since GBE activity associated with APBD is characterized by a late-onset, a therapeutic time window during which treatment can be offered has been proposed [9]. Enhancement of glycogen branching activity and cessation of the accumulation of polyglucosan has been proposed as a potential treatment strategy. Inhibition of the glycogen synthase (GYS) activity, which would alter the GYS/ GBE activity ratio and halt glycogen synthesis and polyglucosan buildup, is an alternative strategy. Guaiacol, an inhibitor of GYS, constitutes a promising candidate for future therapy as preliminary studies in animal models with APBD showed reduced accumulation of polyglucosans and GBE activity in cardiac, liver, and peripheral nerve tissues with no reported adverse effects [9]. There is also limited evidence that anaplerotic dietary therapy with triheptanoin may slow disease progression. Limited functional improvement was observed in a small number of affected individuals in the early stages of the disease, whereas other studies report no benefit [10].

IV. Conclusion

APBD is a rare disorder that can affect the nervous system and present with a variety of neurological symptoms. In this report, we describe an adult patient with an atypical presentation of APBD. The diagnosis can be challenging due to normal imaging and clinical features with alternative neurological conditions. The diagnosis can be made with the constellation of clinical presentation, imaging features, and peripheral nerve biopsy and confirmed with genetic testing. Although most diagnosed patients are of an Ashkenazi Jewish ancestry, APBD is a pan-ethnic disorder. Treatment is mainly supportive.

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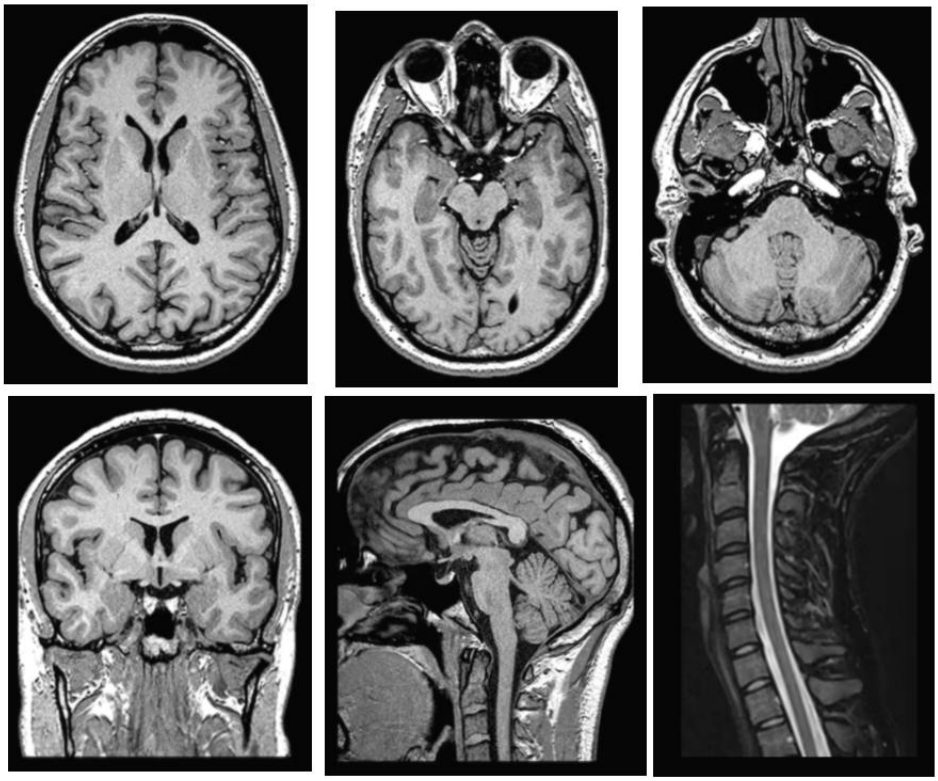

Figure-1: MRI brain and cervical spine showing normal findings

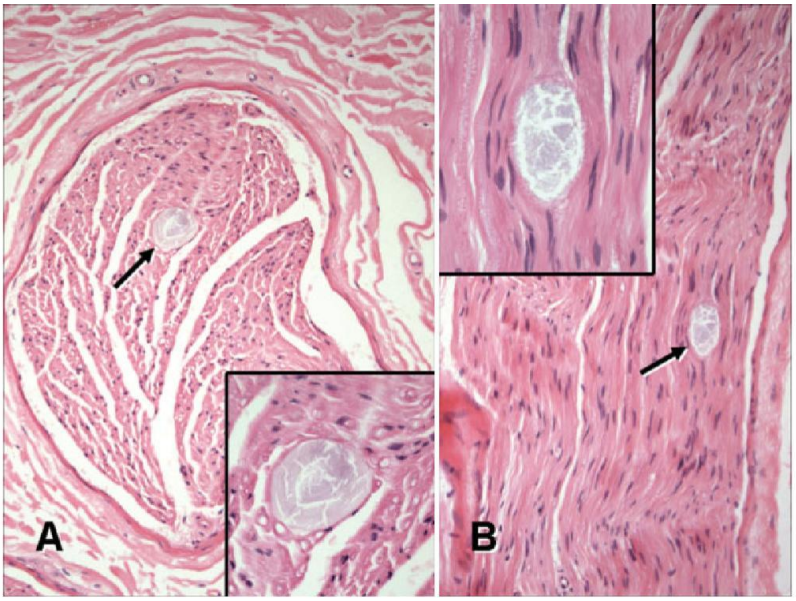

Figure-2: Sural nerve biopsy showing polyglucosan bodies (arrows) in nerve fibers cut in cross-section (A) and longitudinally (B). Insets: Higher magnification of polyglucosan bodies in nerve fibers. (A & B: Hematoxylin and eosin [H&E] stain, original magnification 100. Insets: H&E stain; original magnifications 400.)