Adult Polyglucosan Body Disease: Natural History and Key MRI Findings

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Abstract

Objectives: Adult polyglucosan body disease (APBD) is an autosomal recessive leukodystrophy characterized by neurogenic bladder, progressive spastic gait and peripheral neuropathy. Polyglucosan bodies accumulate in the CNS and PNS and are often associated with glycogen branching enzyme (GBE) deficiency. To improve clinical diagnosis and enable future evaluation of therapeutic strategies, we conducted a multinational study of the natural history and imaging features of APBD. *Methods*: We gathered clinical, biochemical and molecular findings in 50 APBD patients with GBE deficiency from Israel, the United States, France and the Netherlands. Brain and spine MRIs were reviewed in 44 patients. *Results*: The most common clinical findings were neurogenic bladder (100%), spastic paraplegia with vibration loss (90%), and axonal neuropathy (90%). The median age for the onset of neurogenic bladder symptoms was 51, for wheelchair dependence 63 and 70 for death. As the disease progressed, mild cognitive decline may affect up to half of the patients. Neuroimaging showed hyperintense white matter abnormalities on T2 and FLAIR sequences predominantly in the periventricular regions, the posterior limb of the internal capsule, the external capsule and the pyramidal tracts and medial lemniscus of the pons and medulla. Atrophy of the medulla and spine was universal. p.Y329S was the most common *GBE1* mutation, present as a single heterozygous (28%) or homozygous (48%) mutation. *Interpretation*: APBD with GBE deficiency, with occasional exceptions, is a clinically homogenous disorder that should be suspected in patients with adult-onset leukodystrophy or spastic paraplegia with early onset of urinary symptoms and spinal atrophy.

Introduction

Adult polyglucosan disease (APBD) is a rare neurogenetic disorder that is clinically characterized by progressive pyramidal paraparesis, distal sensory deficit in the legs and neurogenic bladder beginning in the 5th or 6th decade of life.[1-3] The motor and sensory abnormalities are related to a combination of myelopathy with peripheral neuropathy.[4] After about a decade of slow functional deterioration, most patients lose independent walking, and thereafter develop involvement of the arms.[3, 5] The disease often leads to premature death.[6-9]

The pathological hallmark of APBD is intracellular accumulation of polyglucosan bodies – containing amylopectin-like polysaccharide – in the central and peripheral nervous system and in other tissues.[1, 9-13] Additional neuropathological findings include cerebral demyelination and gliosis, and loss of myelinated nerve fibers in peripheral nerves. These findings led to the discovery that most patients with APBD have an allelic form of the glycogen storage disease type IV (GSD-IV) caused by glycogen branching enzyme (GBE) deficiency (MIM 232500).[14-17] While the presence of polyglucosan bodies in skin, muscle or nerve tissues suggests the diagnosis, APBD is primarily confirmed by a significant reduction of GBE enzymatic activity in peripheral blood leukocytes or cultured skin fibroblasts.

However, the spectrum of GBE deficiency is broader than APBD since GSD-IV patients can present either with a liver disease, usually in infancy, or a neuromuscular disease.[16] The neuromuscular presentation of GSD-IV is heterogeneous, and 4 main variants have been described depending on the age at

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onset:[16, 18, 19] (i) a perinatal form with multiple congenital contractures, hydrops fetalis, and perinatal death; (ii) a congenital form with hypotonia, muscle wasting, neuronal involvement, inconsistent cardiomyopathy, and death in early infancy; (iii) a childhood form dominated by myopathy or cardiopathy; and (iv) an adult form presenting either as an isolated myopathy or as APBD.

The majority of APBD patients with GBE deficiency are of Ashkenazi Jewish ancestry and have a homozygous p.Y329S mutation in the *GBE1* gene.[3, 15, 17] Overall, the frequency of all glycogen storage diseases is 1:10,000 with GBE deficiency constituting about 3% of all glycogen storage diseases.[16] Less than 50 patients with APBD have been described in the English medical literature. However, this disease is considered to be underdiagnosed.[2, 3, 17]

There is a critical lack of comprehensive overviews of the natural history and the neuroimaging features of APBD. Published clinical and imaging data are based on isolated case reports[2, 20, 21] and small case series.[1, 14, 15] Therefore, to improve the accuracy of clinical diagnosis and to enable future evaluation of therapeutic strategies, we conducted a multinational study of the clinical findings and neuroimaging features of APBD.

Material and Methods

Patients

Clinical and laboratory data have been retrospectively collected from 50 APBD patients, i.e. 47 families, confirmed either by enzymatic and/or molecular testing from 4 reference centers in neurogenetics and neurometabolism in Israel (Hadassah-Hebrew University Medical Center, Jerusalem), the United States (Baylor Research Institute, Dallas, TX), France (La Salpêtrière University Hospital, Paris) and the Netherlands (Center for White Matter Disorders, VU University Medical Center, Amsterdam). The study was approved by local Ethics Committees and written informed consent was obtained for patients or their legal guardians as appropriate (NCT00947960). Neurological examination of all patients was conducted by experienced investigators from the study.

GBE enzymatic activity was measured in leukocytes – or fibroblasts – as described.[14, 22] The sequencing of the *GBE1* gene was limited to exons and intron-exon junctions.[15, 23] Biochemical and molecular analyses were done in different laboratories.

Scoring of brain and spine imaging

The imaging was reviewed by a neurologist expert in white matter diseases (RS) and a specialist in genetic metabolic disorders (FM) according to a standardized form.[24] The main items that were scored comprised: the topography – lobe and region – and aspect of white matter abnormalities, the topography of brain or spinal atrophy, the occurrence of gray matter lesions, contrast enhancement or restricted diffusion.

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Statistics

For the Kaplan-Meier analyses, we assumed that patients are determined to have

APBD at birth. Therefore all time to event data (e.g. time to bladder dysfunction, time

to using a wheel-chair) assumed that the initial time was the date of birth. The

censoring time was the age at latest neurological exam. Finally, the symptoms were

communicated via the caregiver or the patient directly. Differences between men and

women were tested using log-rank test as well.

Results

Clinical presentation

The clinical characteristics of our APBD cohort are described in Table 1. Although most of the patients were of Ashkenazi Jewish background, it appears that APBD is likely to be panethnic. We identified patients of Latin American, Pacific Islander, Caucasian and Cambodian backgrounds. All but three APBD patients developed their symptoms after age of 40; these subjects were of non-Jewish background. They include a male patient, previously published as having a mild hepatic form of GSD-IV, who in his early 30's developed typical APBD,[25] and a 35-year old female patient who presented with a subacute stroke-like episode.

Bladder dysfunction was usually the first symptom that patients developed – 50% of patients were likely to develop it by age 51 years (Figure 1), a few years before developing gait difficulties at a median age of 53. Although in the present study we did not systemically ask men about sexual function, impotence was a common complaint. These two cardinal clinical signs, neurogenic bladder and gait disturbance, were followed in the majority of patients by paresthesias and hypoesthesia, most prominently in the legs (Figure 1) – at a median age of 54 years. By age 62, 50% of patients were likely to need a walker, and by the median age 63 they needed a wheelchair for ambulation (Figure 1). In addition, almost half of APBD patients had mild attention and memory deficits as assessed by bedside neurological examination. Overall, patients with ABPD had a median survival probability of 70 years (Figure 1), which is about 8 years less than the general population (http://www.fis.org/public/survivalcurve-2010.html). There was no difference between

men and women. In addition, affected siblings – i.e. 8 patients from 3 families – followed the same disease course overall.

On the more detailed neurological examination, some APBD patients showed a saccadic pursuit and occasional absence of convergence. Examination of the upper extremities tended to be normal with only tendon reflex abnormality (Table 1). Lower extremities usually showed weakness in an upper motor neuron distribution sometimes associated with distal weakness, deficit in vibration sense, and tendon reflex abnormalities reflecting the myelopathy and sensorimotor peripheral neuropathy. Gait was often spastic and unsteady. In some patients, gait became parkinsonian-like in advanced stages of the disease (Table 1). When assessed by physicians, almost a third of the patients presented with orthostatic hypotension (Table 1). In addition, six patients reported noteworthy diurnal fluctuations of motor symptoms (data not shown).

Electromyogram and nerve conduction studies results were available in 47 patients. Forty-two patients (89%) presented with a sensorimotor polyneuropathy characterized by markedly reduced compound motor action potentials and sensory nerve action potentials with, often, moderately reduced conduction velocities. In most patients, prolonged F-wave latencies in nerves with relatively normal conduction as well as signs of denervation using proximal needle EMG studies indicated an additional proximal involvement. These findings were suggestive of a predominantly axonal polyradiculoneuropathy. When performed (n=13), sural nerve biopsies were always diagnostic and showed abundant intra-axonal polyglucosan bodies. Muscle

biopsies (n=12) were normal or showed only signs of denervation, except in 2

patients in whom polyglucosan bodies were identified in myocytes.

Biochemical and molecular analyses

APBD diagnosis was confirmed based upon a reduction of GBE enzymatic activity in

leukocytes or fibroblasts below 25% of controls (n=43 patients) or the identification of

GBE1 mutations (n=46 patients) or both (n=39 patients). For the 7 ABPD patients

without enzymatic testing, *GBE1* mutations were identified on both alleles. Among

the 4 APBD patients for whom mutational analyses could not be performed or need

further molecular validation, all had a reduction of GBE activity in the range of 10-

20% of normal in addition to intracellular accumulation of polyglucosan bodies in

nerve or muscle tissues.

Mutations of *GBE1* were tested for in 46 patients (Table 1). Mutations on both alleles

were identified in 33 patients (72%), but in 13 patients (28%) only one mutation was

found. By far the most common mutation was p.Y329S, which was present in 35

patients (76%) at a homozygous (n=22) or heterozygous state (n=13) and exclusively

found in Ashkenazi Jewish patients (Table 1). Patients who were only heterozygous

for the p.Y329S mutation had the same disease characteristics including GBE

deficiency usually in the range of 10-20% of normal and clinical abnormalities as

patients who were homozygous for the same mutation. In addition, none of the

patients' parents available for examination had neurological symptoms suggestive of

APBD.

In 2 Ashkenazi Jewish patients, the p.Y329S mutation was found in combination with mutations previously identified in GSD-IV patients (Table 1) presenting with a hepatic form of the disease – p.L224P mutation[26] and p.R565Q mutation (R. Froissart, unpublished data). One patient from the Pacific Islands also carried a p.Y329S mutation together with a frameshift c.2003delA mutation leading to a premature Stop codon (Table 1). Of note, the amino acid at position 329 is commonly involved in APBD. Indeed, besides the most common p.Y329S mutation, a p.Y329C mutation was found in 4 Ashkenazi Jewish patients and one Caucasian patient in combination with a p.N556Y mutation (Table 1). Homozygous p.E242Q mutations were also found in 3 related Latin American patients (Table 1). To our knowledge, these latest mutations – p.R565Q, c2003delA, p.Y329C, p.N556Yand p.E242Q – have not been reported (http://www.hgmd.cf.ac.uk/ac/all.php). The four novel missense mutations are likely pathogenic: they affect conserved residues of the GBE protein and are predicted to alter protein function (http://genetics.bwh.harvard.edu/pph/), segregate with disease in families, are absent from control sequences (http://browser.1000genomes.org/index.html and http://www.ncbi.nlm.nih.gov/projects/SNP) and are associated with significantly reduced GBE enzymatic activity.

Three patients of non-Jewish background presented with atypical symptoms. One patient manifested Alzheimer-like dementia together with axonal neuropathy but normal gait and was a compound heterozygote for p.Y329C and p.N556Y mutations. The other 2 patients presented with subacute symptoms related to a stroke-like episode for one and diaphragmatic failure for the other. The common p.Y329S mutation was not found in these 2 patients; further mutational analyses are in

progress. In these 2 patients, the diagnosis was suspected on the basis of the MRI

pattern and confirmed by the accumulation of polyglucosan bodies in peripheral

tissues and decreased GBE enzymatic activity to 10-20% of normal in leucocytes.

Cerebral and spinal MR characteristics

Brain and spine MRIs were available for review in 44 out of 50 APBD patients. In

general, patients with APBD tended to have a very similar MRI pattern (Table 2). The

most consistent abnormalities were medullary and spinal atrophy that were present in

all the patients (Figure 2A, Table 2). In one patient, this was initially the only finding

despite significantly reduced GBE activity in leukocytes and homozygosity of the

p.Y329S mutation (Figure 3). Cerebellar vermis and, less frequently, hemispheric

atrophy were present in various degrees in most patients (Figure 2A). A thin corpus

callosum, usually mild, was a common feature as well. With the exception of the

patient mentioned above, who only had medullary and spinal atrophy when she was

diagnosed (Figure 3), hyperintense white matter abnormalities on T2 and FLAIR

sequences were always present in the medulla and pons, usually in the pyramidal

tracts and the medial lemniscus (Figure 2B, Table 2). In the cerebral hemispheres,

white matter lesions tended to be symmetric, usually in the periventricular areas and

mostly with occipital predominance (Figure 2B, Table 2). The temporal lobes were

also frequently involved (Figure 2B). Lesions were confluent or multifocal, but often

both (Figure 2B, Table 2). The external capsule and the posterior limb of the internal

capsule were often affected while the anterior limb was spared (Figure 2B, Table 2).

The abnormal white matter areas had normal or hypointense signal on T1-weighted

images (data not shown).

Discussion

We present the largest series of 50 APBD patients, which allowed us to delineate the

natural history of the disease and depict the singular MRI pattern of APBD. Although

most patients were of Ashkenazi Jewish origins, the diagnosis of APBD should also

be considered in other ethnicities.[27] Neurogenic bladder, spastic paraplegia and

axonal neuropathy are cardinal signs of the disease and present in 90% of the

patients. Of note, bladder dysfunction is often the initial symptom, sometimes starting

one or two decades before any difficulty walking or sensory deficit. This likely

correlates with the degree of medullary and spinal atrophy that was observed in all

APBD patients,[2, 28] even in the context of little or no cerebral white matter

abnormalities. Therefore, APBD should be suspected in any adult patient with spastic

paraplegia and significant neurogenic bladder symptoms associated with spinal

atrophy. Besides the medullary and spinal atrophy, the demyelinating leukodystrophy

in APBD is usually characterized by distinguishing features such as lesions of the

posterior limb of the internal capsule, the external capsule and the pyramidal tracts

and medial lemniscus of the pons and medulla. Cognitive decline consisting of mild

attention and memory deficit may also affect up to 50% of patients with APBD. Only

one patient manifested Alzheimer-like dementia. However, standardized

neuropsychological testing not routinely used in this study is needed to further

evaluate cognitive functions. Moreover, occasional subacute presentations and

significant fluctuations of symptoms present in some APBD patients suggest that, as

in most other glycogen storage diseases, decreased glycogen degradation may lead

to energy deficit.

The most common differential diagnoses of APBD are multiple sclerosis, hereditary

spastic paraplegia, adrenomyeloneuropathy and, in men with early urinary

symptoms, prostate hypertrophy. In older patients, differential diagnoses of APBD

may include white matter leukoencephalopathies due to severe hypertension or

NOTCH3 mutation.[29] Due to the occasional late occurrence of bradykinesia,

orthostatic hypotension and cerebellar symptoms, some patients may be

misdiagnosed with multiple system atrophy. Although there have been some reports

of APBD patients resembling amyotrophic lateral sclerosis,[30] we did not have any

patient presenting with a motor neuron disease amongst our cohort. In addition, a

few patients were diagnosed despite an atypical clinical presentation, i.e. Alzheimer-

like dementia, a stroke-like episode and a respiratory failure due to diaphragmatic

dysfunction. Notably, these 3 patients were of non-Jewish descent and their

diagnosis was initially suspected solely based on imaging findings. Notwithstanding

Alexander disease, autosomal dominant leukodystrophy associated with *LMNB1*

duplication and leukoencephalopathy with brainstem and spinal cord involvement

and lactate elevation (LBSL due to *DARS2* mutations) can also present with

medullary and spinal atrophy – but also signal abnormalities of the spinal cord in

LBSL –,[31-33] we are not aware of other leukodystrophies presenting with a similar

pattern of white matter lesions on MRI.

Although APBD patients showed a reduction to usually less than 25% of GBE activity

– unlike the 50% activity measured in non-manifesting carriers –, in about a third of

the patients, only one mutation (p.Y329S) was identified despite standard

sequencing of the whole gene. However, large deletions, splice mutations or

mutations in regulatory regions of *GBE1* were not searched in this study but are not

excluded. For example, in one APBD patient heterozygous for the mutation p.Y329S at the genomic level, cDNA sequencing revealed only one mutated allele, indicating that the second allele is missing (Supplementary Figure 1). Transient expression experiments showed that the significant retention of GBE activity in the p.Y329S allele may be a reason for the mild disease compared to other GSD-IV phenotypes.[26] Indeed, more than 80% of the patients in our series harbored the p.Y329S Jewish mutation.

The mechanism by which GBE deficiency causes a neurological disorder is not known.[34] One hypothesis states that the polyglucosan inclusions mechanically disrupt normal cellular function such as intra-cellular transport. Since astrocytes are primarily involved in brain glycogen synthesis and utilization,[35] another hypothesis is that decreased glycogen degradation leads to energy deficit in glial cells and therefore neurons. Here we report the first GSD-IV patient who initially presented with a mild GSD-IV hepatopathy and later developed typical symptoms of APBD.[25] This emphasizes that there is a wide spectrum of clinical presentations that may be related to varying amounts of residual GBE enzymatic activities in target tissues and/or associated variants in other enzymes involved in glycogen synthesis or degradation.

In conclusion, this study provides the first quantitative natural history of APBD and opens ways to future therapeutic trials aimed at slowing or reversing disease progression. The delineation of the key MRI findings of ABPD should lead to a better and earlier recognition of the disease, even when the cardinal signs are missing.

Acknowledgements

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Figure legends

Figure 1: Kaplan-Meier analyses indicating the natural history of 50 APBD patients

for time to bladder dysfunction, difficulty walking, use of a wheelchair and death.

Figure 2: Typical cerebral and spinal pattern in APBD patients. (A) T1 sagittal scans

showing important medullary and spinal atrophy and mild vermian atrophy; (B) FLAIR

axial scans showing hyperintense white matter abnormalities in the periventricular

regions, with occipital predominance, the external capsule and the posterior limb of

the internal capsule (dashed circles), the medial edges of the inferior and middle

cerebellar peduncles (arrows) and in the pyramidal tracts and medial lemniscus of

the medulla and pons (plain circles).

Figure 3: APBD patient with medullary atrophy but normal white matter matter in the

early stages of her disease.

Table 1: Clinical and molecular findings in a cohort of 50 APBD patients. All ages are indicated as means, ±SD and ranges.

UL: upper limbs; LL: lower limbs.

Demographic			
- Gender	Female: 23 (47%)	Male: 27 (53%)	
- Ethnicity	Ashkenazi: 37 (73%)	Other Jews: 5 (12%)	Other: 8 (15%)
Age at onset (years)			
- Bladder dysfunction (n=50)	51±10 (20-71)		
- Difficulty walking (n=44)	53±5 (33-65)		
- Paresthesia (n=24)	53±6 (34-64)		
Motor handicap, age at onset (years)			
- walk with one cane (n=29)	58±4 (51-65)		
- walk with two canes (n=10)	60±5 (53-68)		
- walk with walker (n=26)	63±4 (55-70)		
- wheel chair bound (n=24)	64±6 (51-73)		
Age at examination (years)	59±7 (36-72)		
Disease duration (years)	9±7 (2-40)		
Neurological examination			
- Romberg	Positive: 14(37%)	Borderline: 9 (24%)	Negative: 15 (39%)
- Tandem	Unable: 28 (62%)	Abnormal: 14 (31%)	Normal: 3 (7%)
- LL spasticity	Yes: 45 (90%)		
- UL spasticity	Yes: 6 (12%)		

- LL reflexes (knee)	Increased: 23 (46%)	Decreased/Absent: 15 (30%)	Normal: 12 (24%)
- LL reflexes (ankle)	Increased: 6 (12%)	Decreased/Absent: 40 (80%)	Normal: 4 (8%)
- UL reflexes	Increased: 15 (30%)	Decreased/Absent: 9 (18%)	Normal: 26 (52%)
- Plantar reflexes	Extensor: 48 (96%)		Flexor: 2 (4%)
- LL vibration sense	Decreased: 46 (94%)		Normal: 3 (6%)
- UL vibration sense	Decreased: 14 (29%)		Normal: 35 (71%)
- Attention deficit	Yes: 24 (48%)		
- Memory deficit	Yes: 23 (46%)		
Eye movement abnormalities			
- Pursuit	Saccadic: 18 (39%)		Normal: 28 (61%)
- Voluntary saccades	Slow: 9 (20%)		Normal: 37 (80%)
Other features	Orthostatic hypotension: 10 (31%)	Cerebellar symptoms: 8 (16%)	Bradykinesia: 7 (14%)
Molecular findings **(percent of 46 patients)**	Homozygous p.Y329S: 22 (48%)	Heterozygous p.Y329S: 13 (28%)	Other: Heterozygous p.Y329S/p.L224P: 1 Heterozygous p.Y329S/p.R565Q: 1 Heterozygous p.Y329S/c.2003delA:1 Heterozygous p.Y329C/p.N556Y: 5 Homozygous p.E242Q: 3 (related)

Table 2: Main brain and spine MRI features analyzed in a cohort of 44 APBD patients.

| Age (years)	58±7 (39-73)			
White matter (WM) lesions				
- Predominant affected regions	Periventricular **68%**	Deep 9%	Subcortical 7%	*None 16%*
- Predominant affected lobes	Occipital **54%**	Parietal 7%	*None 39%*	
- Capsules	Internal_post limb **77%**	Internal_ant limb 7%	External **67%**	
- Cerebellum	Hilus dentatus 30%	Inf peduncle 21%	Mid peduncle 23%	Sup peduncle 14%
- Midbrain	Med lemniscus **89%**	Pyramidal tract **95%**		
- Pons	Med lemniscus **93%**	Pyramidal tract **91%**		
- Medulla	Decussatio (ML) **95%**	Pyramidal tract **98%**		
Aspect of WM lesions	Confluent **84%**	Multifocal 70%	Symmetrical **86%**	
Atrophy				
- Ventricles (enlarged)	32% (11% mild)			
- Cerebral spaces (increased)	18% (7% mild)			
- Corpus callosum	51% (23% mild)			
- Cerebellum hemispheres	14%			
- Vermis	70% (20% mild)			
- Medulla oblongata	**100%**			
- Spine	**100%**			

Figure 1
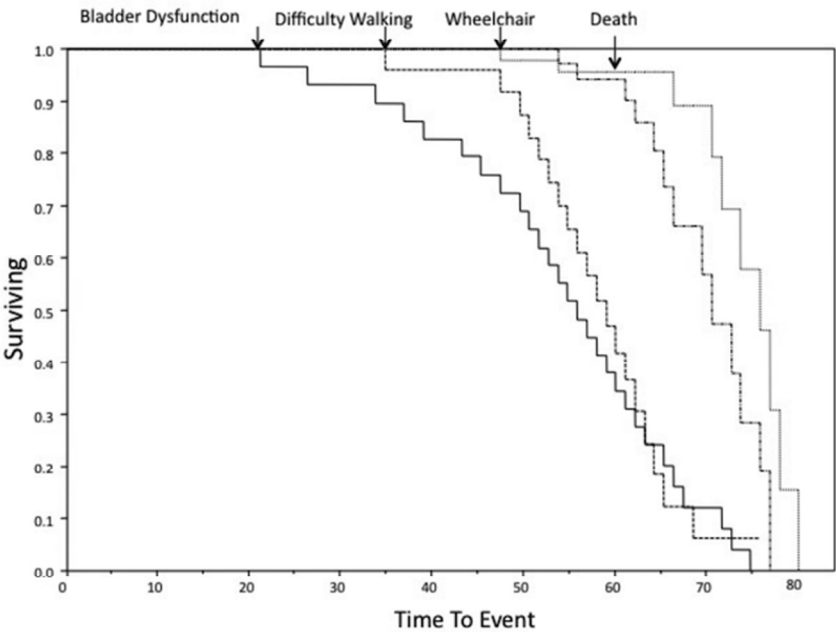
Figure 1: Kaplan-Meier analyses indicating the natural history of 50 APBD patients for time to bladder dysfunction, difficulty walking, use of a wheelchair and death.
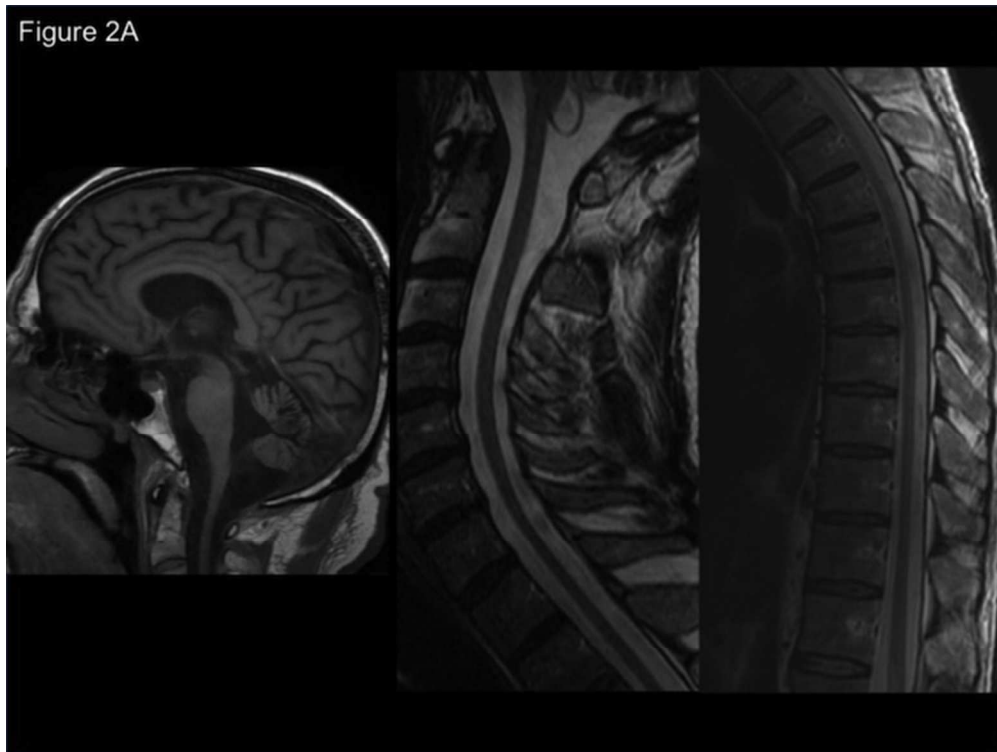65x48mm (300 x 300 DPI)

Figure 2A: Typical cerebral and spinal pattern in APBD patients. (A) T1 sagittal scans showing important medullary and spinal atrophy and mild vermian atrophy.
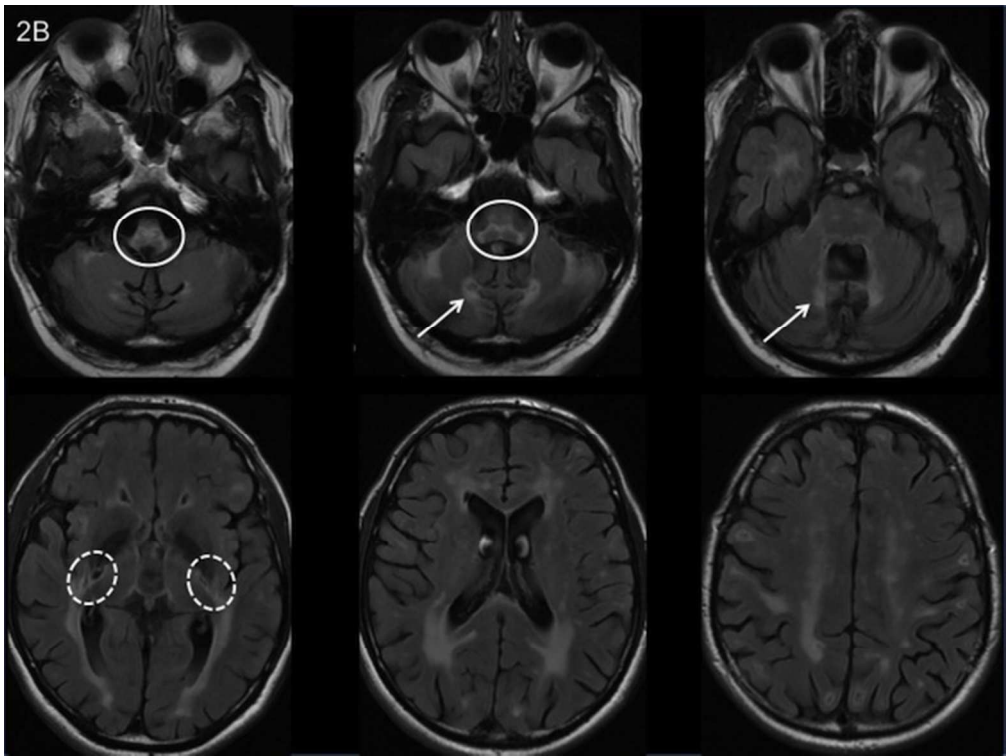65x48mm (300 x 300 DPI)

Figure 2(B): FLAIR axial scans showing hyperintense white matter abnormalities in the periventricular regions, with occipital predominance, the external capsule and the posterior limb of the internal capsule (dashed circles), the medial edges of the inferior and middle cerebellar peduncles (arrows) and in the pyramidal tracts and medial lemniscus of the medulla and pons (plain circles).
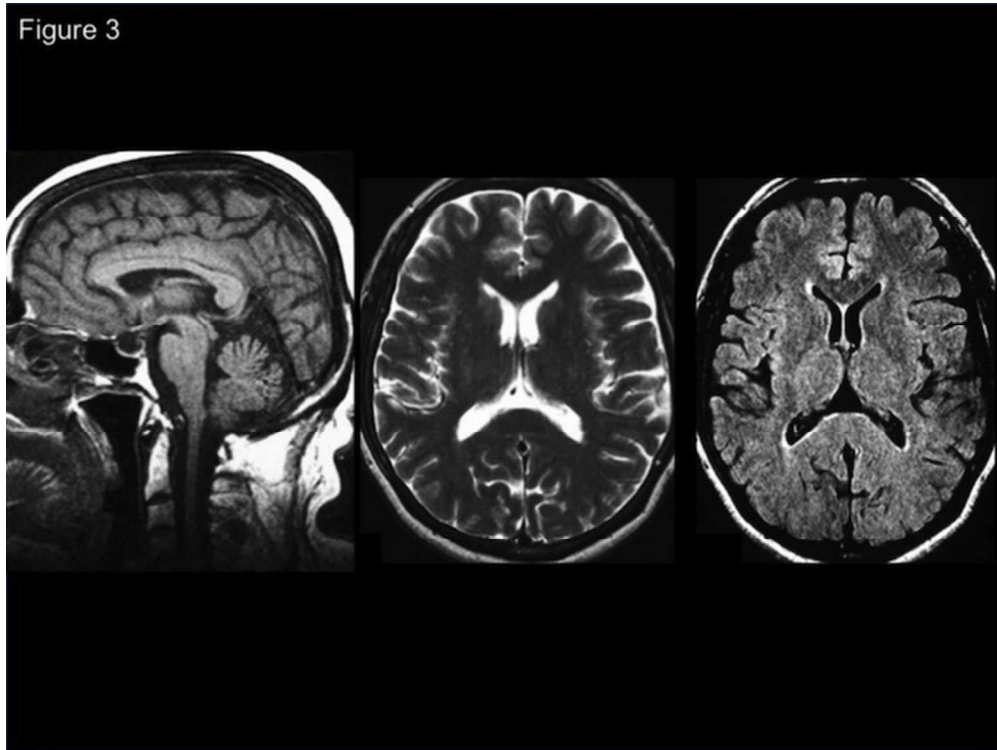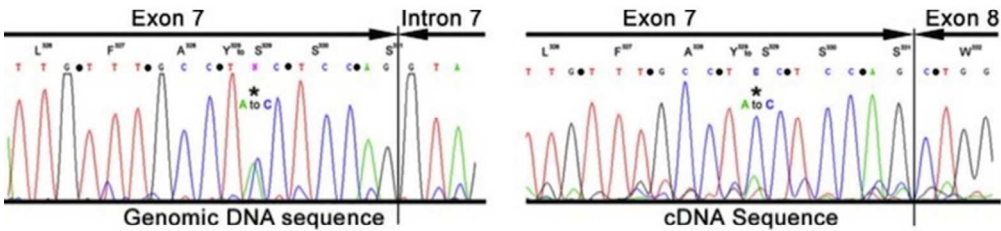65x48mm (300 x 300 DPI)

Figure 3: APBD patient with medullary atrophy but normal white matter matter in the early stages of her disease.
65x48mm (300 x 300 DPI)

Supplementary Figure 1

Electropherogram of an APBD patient showing *GBE1* genomic DNA and cDNA; both were isolated from peripheral blood lymphocytes. The asterisk indicates the change in the 329th codon of *GBE1*. Genomic DNA indicates a heterozygous p.Y329S mutation. However, cDNA reveals only one mutated allele, indicating that the second allele is missing.

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