

FOR PHYSICIANS AND MEDICAL PROFESSIONALS

Adult Polyglucosan Body Disease An Overview



DESCRIPTION

Adult polyglucosan body disease (APBD) is a rare, autosomal recessive neurogenic disorder. APBD manifests clinically with lower extremity spasticity and sensorimotor polyneuropathy and is frequently mistaken for multiple sclerosis, hereditary spastic paraplegia, adrenomyeloneuropathy, amyotrophic lateral sclerosis, or metachromatic leukodystrophy. Men with urinary symptoms, an early manifestation of APBD, may also be mistaken for having an enlarged prostate.

APBD results from a mutation of the glycogen branching enzyme gene (GBE1). This gene is responsible for introducing normal glucose branches to the growing glycogen molecule during glycogen synthesis. Loss of GBE1 activity results in glycogen storage disease type IV (GSD IV), which is known as Andersen's Disease in children. In adults GBE deficiency results in a signature sign – the deposition of relatively insoluble amylopectin-like glycogen called polyglucosan bodies in peripheral nerves. Unlike glycogen, polyglucosan bodies cannot be utilized by the body as an energy source and build up in the nerves leading to damage over time.

APBD is seen worldwide, most commonly in Jewish people of Ashkenazi (Eastern European) ancestry, with an estimated carrier rate in this group of 1:48. Of the many mutations that cause APBD, most Ashkenazi Jewish patients have a homozygous presentation of the p.Y329S mutation. The second most common mutation seen in Ashkenazi Jews is a deep intronic mutation found in compound heterozygous presentation with the p.Y329S mutation.

Due to its monogenic basis there is great promise for the development of therapeutic solutions for APBD. Therapeutic techniques now under development for treatment of APBD may later show application to other glycogen storage diseases.



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CLINICAL SIGNS AND SYMPTOMS

Clinical signs and symptoms suggestive of APBD typically manifest around the fifth decade of life, although symptoms can present as early as the late 30's. The severity of symptoms varies greatly from one person to another. The first sign is frequently neurogenic bladder, including increased need to urinate in a progressive manner that may lead to urinary incontinence. Patients may also present initially with gait problems and peripheral neuropathy.



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Some affected individuals develop mild cognitive impairment; however, for some patients cognitive function may continue to decline. For these patients, dementia can be the end result.

A retrospective investigation into the frequency of misdiagnosis uncovered an approximate 6.8 year delay in the proper diagnosis of APBD.* The study revealed that 100% of the patients questioned had an initial misdiagnosis of their symptoms. These patients finally received a proper diagnosis through a combination of clinical and imaging findings, which include findings of reduced glycogen branching enzyme activity and testing for GBE1 mutations.

**Hellmann MA1, Kakhlon O, Landau EH, Sadeh M, Giladi N, Schlesinger I, Kidron D, Abramsky O, Reches A, Argov Z, Rabey JM, Chapman J, Rosenmann H, Gal A, Moshe Gomori J, Meiner V, Lossos A. "Frequent misdiagnosis of adult polyglucosan body disease." J Neurology, 2015 Oct;262(10):2346-51. doi: 10.1007/s00415-015-7859-4. Epub 2015 Jul 21.*

DIAGNOSIS

Clinical diagnosis is typically made by genetic screening and confirmed through biochemical testing of GBE activity in blood or muscle cells if necessary. Genetic screening commonly includes sequencing of the GBE1 gene, either alone, as part of a gene panel, or as part of genomic sequencing test such as whole exome or whole genome sequencing. There are approximately 37 specialized laboratories worldwide that offer gene screening for APBD. MRI of the brain shows white matter changes in the CNS and may serve as an additional diagnostic tool. A recently proposed investigation is seeking to apply MRI as a measure of treatment efficacy.

DISEASE MANAGEMENT

Current management of APBD symptoms is individualized for each patient. Treatment generally requires a team approach and may include neurologists, internists, urologists and rehab specialists.

Management focuses on:

- Use of gait safety devices;
- Antispasmodic bladder medications;
- In-and-out bladder catheterization or an indwelling bladder catheter;
- Behavioral modification and cognitive aids.

RESEARCH DIRECTIONS

Glycogen synthase is an essential component of glycogen production along with glucose branching by the GBE1 gene. Presently pre-clinical studies for treatment of APBD include the following:

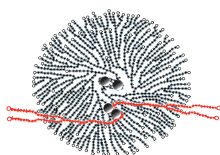
- Adeno-associated viral (AAV) vector to deliver GBE1 DNA into affected tissues;
- Glycogen synthase inhibition through utilization of antisense oligoneucleotide degradation of targeted mRNA, and also pharmaceuticals such as Guaiacol;
- Small molecule applications development by high throughput screening, which has recently uncovered other promising anti-synthase candidates.
- TGM5, a form of triheptanoin to stabilize the GBE protein with the p.Y329S mutation.

APBD RESEARCH FOUNDATION

Founded in 2005, the APBD Research Foundation is the only nonprofit organization in the United States dedicated to helping patients with APBD. The Foundation works to improve the diagnosis and treatment of APBD, support individuals and families affected by the disease, and increase awareness of APBD among the medical community and the public. Operating almost entirely on the efforts of volunteers and guided by a Scientific Advisory Board, the Foundation has identified and awarded over \$1 million in grants to leading researchers in five countries aimed at developing treatments and a cure.



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APBD

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RESEARCH FOUNDATION

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