Diagnosis and Management of Glycogen Storage Disease Type IV, Including Adult Polyglucosan Body Disease: A Clinical Practice Resource

ABSTRACT

Glycogen storage disease type IV (GSD IV) is an ultra-rare, autosomal recessive disorder caused by pathogenic variants in *GBE1*. Reduced or deficient glycogen branching enzyme activity occurs, and glycogen synthesis is impaired. Ultimately, poorly-branched glycogen called polyglucosan accumulates and aggregates into deposits called polyglucosan bodies. GSD IV is a clinically heterogeneous disorder with presentations in utero, during infancy, in early childhood, in adolescence, or in middle to late adulthood (the latter referred to as Adult Polyglucosan Body Disease, or APBD). This Guideline is the first consensus on diagnosing and managing patients with GSD IV, including APBD.

BACKGROUND

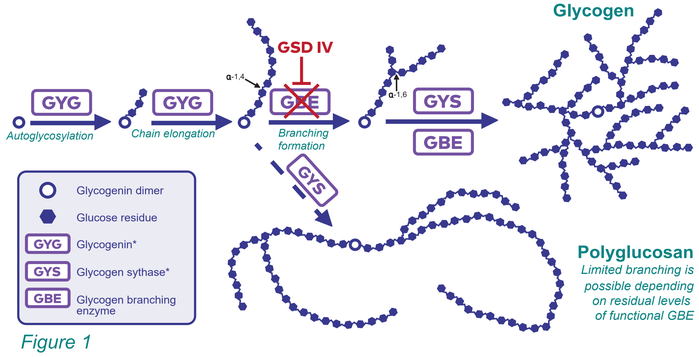


Figure 1

Glycogen serves as a storage form of glucose in humans. Glycogen synthesis takes place in all tissues throughout the body, predominantly in the liver and skeletal muscle. It is stored as large, branched polymers of glucose residues bound through α-1,4 and α-1,6 glycosidic bonds (Fig. 1).

The first enzyme that initiates glycogen synthesis is the homodimer glycogenin (GYG). It auto-glycosylates and initiates the primer glucan chain through which the next enzyme, glycogen synthase (GYS), begins synthesizing glycogen. GYS elongates the chain by adding glucose molecules through α-1,4 linkages. From there, glycogen branching enzyme (GBE) catalyzes the last step in glycogen biosynthesis by transferring α-1,4-linked glycosyl units into an α-1,6 position, thus creating branched chains of glycogen.

In all tissues, GYS and GBE work in concert to synthesize the spherical, branched glycogen structure with short, peripheral chains conferring the stability and solubility of glycogen.

When GBE activity is reduced, glycogen synthesis is impaired. Indeed, the continued action of GYS elongates the linear α-1, 4 glycosidic chains but without the normal pattern of α-1,6 branch points. The linear chains tangle and form double helices, resulting in the formation of abnormally structured glycogen called “polyglucosan.” Tight packing of the double helices induces crystallization and renders the polyglucosan water-insoluble.

Polyglucosan accumulates and aggregates in deposits referred to as “polyglucosan bodies (PBs).” The PBs disrupt cellular function. For example, in the case of neurons, PBs disturb retrograde and anterograde axonal transport.

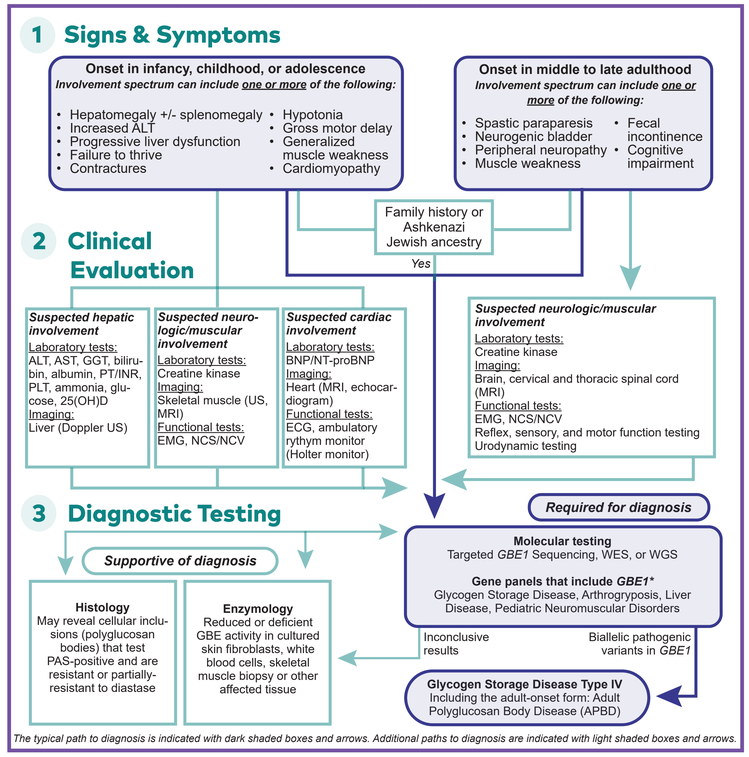
GSD IV:

- ultra-rare autosomal recessive disorder
- 1 in 600,000-800,000 individuals worldwide
- accounts for 3% of all GSDs
- biallelic pathogenic/likely pathogenic variants in glycogen branching enzyme 1 (*GBE1*)
- results in reduced or deficient GBE activity
- impaired glycogen synthesis leads to accumulation of polyglucosan bodies
- clinically heterogeneous disorder with presentations:
  - in utero
  - during infancy
  - early childhood
  - adolescence
  - middle to late adulthood (referred to as APBD)

APBD = Adult-onset Peripheral neuropathy Bladder dysfunction Decreased energy

The National Library of Medicine has recorded approximately 200 cases of APBD worldwide. The disorder is of a particularly high frequency in the Ashkenazi Jewish population where the carrier rate has been calculated to be 1 in 48. Based on this carrier frequency, the APBD Research Foundation estimates the prevalence of APBD at the gene level -- that is, whether the disease is clinically diagnosed or not -- is 3,400 for those of Ashkenazi Jewish ancestry over age 50 years in the United States.

Diagnostic workup will vary depending on the individual patient's phenotype and may include routine clinical laboratory investigations, imaging, electrophysiological tests, and functional assessments.



The typical path to diagnosis is indicated with dark shaded boxes and arrows. Additional paths to diagnosis are indicated with light shaded boxes and arrows.

Figure 2

The confirmatory diagnosis of GSD IV relies on molecular testing of *GBE1* to document biallelic pathogenic variants. Biochemical analysis proving GBE enzyme reduction or deficiency and histopathology of affected tissue(s) is supportive of a GSD IV diagnosis (Fig. 2).

METHODS

In collaboration with the Association for Glycogen Storage Disease in the United States, the APBD Research Foundation, affected patients, and patient advocates, a list of disciplines involved in the management of GSD IV was created. A national group of experts was then assembled to form the “Consensus Development Panel” (Fig. 3)

Consensus Development Panel

19 specialists with expertise in:

- Medical Genetics
- Pediatrics
- Hepatology
- Neurology
- Cardiology
- Physical Rehabilitation
- Urology
- Genetic Counseling
- Dietetics
- Diagnostics
- Enzymology
- Pathology

Figure 3

RESULTS

This Guideline provides practical steps to confirm a GSD IV diagnosis and best practices for medical management, including:

- imaging of the liver, heart, skeletal muscle, brain, and spine
- functional and neuromusculoskeletal assessments
- laboratory investigations
- liver and heart transplantation
- long term follow-up care

GSD IV, including APBD, is a multisystem disorder with variable primary tissue manifestations, including hepatic, muscular, neurologic, and/or cardiac involvement.

Patients present with a wide range of difficult-to-manage symptoms and are best cared for by a multidisciplinary team led by a physician with expertise in this disorder. Team members should include a metabolic disease specialist, a medical geneticist and other specialists dictated by the disease manifestations.

Transplantation specialists should be consulted when indications for liver and/or heart disease arise. All specialists involved in the care of an individual with GSD IV, including APBD, should understand the disease and its broad manifestations. The progression of pediatric-onset GSD IV through adulthood remains unclear. Therefore, longitudinal follow-up is needed, and additional team members may be needed on the multidisciplinary care team if new symptoms arise. Such follow-up is warranted regardless of age at initial presentation or symptoms. The psychological and emotional impact of this disease on the patients, their families, and their caregivers should also be considered.

Disease characterization and recommended clinical surveillance for patients affected by glycogen storage disease type IV (GSD IV) with symptom onset in infancy, childhood, or adolescence.

Specialist	Role in multidisciplinary evaluation
Genetics	Care coordination, interpretation of genetic testing, genetic counseling
Hepatology	Evaluate for onset and progression of hepatic dysfunction and portal hypertension; assess need for liver transplantation
Neurology	Evaluate for onset and progression of abnormal muscle tone, bulk, function, strength, and gait; assess developmental milestone acquisition
Cardiology	Evaluate for onset and progression of cardiomyopathy and/or arrhythmias; assess need for heart transplantation
Rehabilitation Therapy	Longitudinal monitoring of neuromusculoskeletal and cardiorespiratory status including motor control and development, muscle tone, strength, endurance, fatigue, pain, skin integrity, and function, and provision of appropriate direct therapy for management of symptoms, provision of recommendations for exercise and adaptive equipment, and optimization of status and function. Additional rehabilitation specialties (i.e., speech-language pathology, pelvic floor rehabilitation) should be considered based on the individual patient's needs and symptoms.
Nutrition	Provide appropriate dietary recommendations
Behavioral Psychology/ Psychiatry	Evaluate for onset and progression of cognitive delay, decline, or psychiatric manifestations and provision of appropriate management techniques
Urology	Evaluate urinary tract dysfunction and provision of appropriate management techniques, if needed

All patients with GSD IV should undergo comprehensive, multidisciplinary evaluations to assess for and manage hepatic, muscular, neurologic, and cardiac involvement.

Disease characterization and recommended clinical surveillance for patients affected by Adult Polyglucosan Body Disease (APBD).

Specialist	Role in multidisciplinary evaluation
Genetics	Care coordination, interpretation of genetic testing, genetic counseling
Neurology	Evaluate for onset and progression of abnormal muscle tone, bulk, strength, and gait, autonomic testing
Urology	Evaluate urinary tract dysfunction and provision of appropriate management techniques
Rehabilitation Therapy	Longitudinal monitoring of neuromusculoskeletal and cardiorespiratory status including motor control and development, muscle tone, strength,endurance, fatigue, pain,skin integrity, and function, and provision of appropriate direct therapy for management of symptoms, provision of recommendations for exercise and adaptive equipment, and optimization of status and function. Additional rehabilitation specialties (i.e., pelvic floor rehabilitation, speech-language pathology) should be considered based on the individual patient's needs and symptoms.
Behavioral Psychology/ Psychiatry	Evaluate for presence, onset, and progression of cognitive decline, or psychiatric manifestations and provide appropriate management techniques
Cardiology	Evaluate for presence, onset, and progression of cardiomyopathy
Nutrition	Provide appropriate dietary recommendations
Hepatology	Evaluate for presence, onset, and progression of hepatic dysfunction if liver function tests are abnormal

All patients with APBD should undergo comprehensive, multidisciplinary evaluations to assess for and manage neurologic, muscular, cognitive, cardiac, and hepatic involvement.

Figure 4

CONCLUSIONS

GSD IV, including APBD, is a complex, multisystem disorder with variable primary tissue manifestations. Patients present with a wide range of difficult-to-manage symptoms and therefore require comprehensive, multidisciplinary evaluations to assess and treat hepatic, muscular, neurologic, and/or cardiac involvement. Additionally, longitudinal, multidisciplinary follow-up is essential for all patients, regardless of age. It should include experts in medical genetics, hepatology, neurology, physical rehabilitation, cardiology, behavioral psychology, urology, and nutrition.

REFERENCES

Koch RL, Soler-Alfonso C, Kiely BT, et al. Diagnosis and management of glycogen storage disease type IV, including adult polyglucosan body disease: A clinical practice resource. Mol Genet Metab. 2023;138(3):107525. doi:10.1016/j.ymgme.2023.107525

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