

Review article

Diagnosis and management of glycogen storage disease type IV, including adult polyglucosan body disease: A clinical practice resource



Rebecca L. Koch^{a,*}, Claudia Soler-Alfonso^b, Bridget T. Kiely^a, Akihiro Asai^{c,d}, Ariana L. Smith^e, Deeksha S. Bali^a, Peter B. Kang^f, Andrew P. Landstrom^{g,h}, H. Orhan Akmanⁱ, T. Andrew Burrow^j, Jennifer L. Orthmann-Murphy^k, Deberah S. Goldman^l, Surekha Pendyal^a, Areeg H. El-Gharbawy^a, Stephanie L. Austin^a, Laura E. Case^{a,m}, Raphael Schiffmannⁿ, Michio Hiranoⁱ, Priya S. Kishnani^a

^a Division of Medical Genetics, Department of Pediatrics, Duke University Medical Center, Durham, NC, USA

^b Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

^c Department of Pediatrics, University of Cincinnati Medical Center, Cincinnati, OH, USA

^d Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

^e Division of Urology, Department of Surgery, University of Pennsylvania Health System, Philadelphia, PA, USA

^f Paul and Sheila Wellstone Muscular Dystrophy Center, Department of Neurology, University of Minnesota Medical School, Minneapolis, MN, USA

^g Division of Cardiology, Department of Pediatrics, Duke University School of Medicine, Durham, NC, USA

^h Department of Cell Biology, Duke University School of Medicine, Durham, NC, USA

ⁱ Department of Neurology, Columbia University Irving Medical Center, New York City, NY, USA

^j Section of Genetics and Metabolism, Department of Pediatrics, University of Arkansas for Medical Sciences, Arkansas Children's Hospital, Little Rock, AR, USA

^k Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA

^l Adult Polyglucosan Body Disease Research Foundation, Brooklyn, NY, USA

^m Doctor of Physical Therapy Division, Department of Orthopedic Surgery, Duke University School of Medicine, Durham, NC, USA

ⁿ Texas Neurology Group, Dallas, TX, USA

ARTICLE INFO

Article history:

Received 12 December 2022

Received in revised form 20 January 2023

Accepted 22 January 2023

Available online 25 January 2023

Keywords:

Glycogen branching enzyme
Glycogen storage disease type IV
Andersen disease
Adult polyglucosan body disease
Clinical practice guideline
Management guideline
Diagnosis guideline

ABSTRACT

Glycogen storage disease type IV (GSD IV) is an ultra-rare autosomal recessive disorder caused by pathogenic variants in *GBE1* which results in reduced or deficient glycogen branching enzyme activity. Consequently, glycogen synthesis is impaired and leads to accumulation of poorly branched glycogen known as polyglucosan. GSD IV is characterized by a remarkable degree of phenotypic heterogeneity with presentations in utero, during infancy, early childhood, adolescence, or middle to late adulthood. The clinical continuum encompasses hepatic, cardiac, muscular, and neurologic manifestations that range in severity. The adult-onset form of GSD IV, referred to as adult polyglucosan body disease (APBD), is a neurodegenerative disease characterized by neurogenic bladder, spastic paraparesis, and peripheral neuropathy. There are currently no consensus guidelines for the diagnosis and management of these patients, resulting in high rates of misdiagnosis, delayed diagnosis, and lack of standardized clinical care. To address this, a group of experts from the United States developed a set of recommendations for the diagnosis and management of all clinical phenotypes of GSD IV, including APBD, to support clinicians and caregivers who provide long-term care for individuals with GSD IV. The educational resource includes practical steps to confirm a GSD IV diagnosis and best practices for medical management, including (a) imaging of the liver, heart, skeletal muscle, brain, and spine, (b) functional and neuromusculoskeletal assessments, (c) laboratory investigations, (d) liver and heart transplantation, and (e) long-term follow-up care. Remaining knowledge gaps are detailed to emphasize areas for improvement and future research.

Published by Elsevier Inc.

Abbreviations: ACE, angiotensin-converting enzyme; AFP, α -fetoprotein; AGSD, Association for Glycogen Storage Disease; ALS, amyotrophic lateral sclerosis; ALT, alanine aminotransferase; AMPK, AMP-activated protein kinase; APBD, adult polyglucosan body disease; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; ATP, adenosine triphosphate; BNP, B-type natriuretic peptide; CDC, Centers for Disease Control and Prevention; CK, creatine kinase; CNS, central nervous system; DCM, dilated cardiomyopathy; EMG, electromyography; GBE, glycogen branching enzyme; GGT, gamma-glutamyl transferase; Glc4, Hex4, glucose tetrasaccharide; GSD, glycogen storage disease; GSD IV, GSD type IV; GYG, glycogenin; GYS, glycogen synthase; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; HCM, hypertrophic cardiomyopathy; HGMD, Human Gene Mutation Database; ICF, International Classification of Function, Disability, and Health; INR, international normalized ratio; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; MS, multiple sclerosis; NCS, nerve conduction studies; NGS, next-generation sequencing; NPH, normal pressure hydrocephalus; NT-proBNP, N-terminal-pro hormone BNP; OMIM, Online Mendelian Inheritance in Man; PAS, periodic acid-Schiff; PCP, primary care physician; PELD, Pediatric End-Stage Liver Disease; PNS, peripheral nervous system; PT, prothrombin time; RES, reticulo-endothelial system; UCCS, uncooked cornstarch; UNOS, United Network for Organ Sharing; UTI, urinary tract infections; VUS, variants of uncertain significance; WES, whole exome sequencing; WGS, whole genome sequencing; WHO, World Health Organization.

* Corresponding author at: Duke University Medical Center, Box 103857, Durham, NC, USA.

E-mail address: rebecca.koch@duke.edu (R.L. Koch).

Contents

1.	Purpose	2
2.	General background	2
2.1.	Overview	2
2.2.	History	3
2.3.	Clinical variability	3
3.	Methods and process	4
3.1.	Nomenclature	4
3.2.	Consensus development panel	4
3.3.	Target audience	4
4.	Diagnosis	4
4.1.	Differential diagnosis	4
4.2.	Clinical evaluation	7
4.3.	Laboratory evaluation	8
4.4.	Diagnostic testing	8
4.4.1.	Molecular genetic analysis	8
4.4.2.	Biochemical analysis	9
4.4.3.	Histopathology	9
5.	Medical management	9
5.1.	Hepatology	10
5.1.1.	Disease expression	10
5.1.2.	Evaluation and management	11
5.2.	Cardiology	12
5.2.1.	Disease expression	12
5.2.2.	Evaluation and management	12
5.3.	Considerations and indications for liver or heart transplantation	13
5.4.	Neurology	13
5.4.1.	Disease expression	13
5.4.2.	Evaluation and management	14
5.5.	Urology	15
5.5.1.	Disease expression	15
5.5.2.	Evaluation and management	15
5.6.	Rehabilitation therapy	16
5.7.	Fatigue and physical activity	17
5.8.	Psychology	17
5.9.	Care, coordination, and support	18
5.10.	Genetic counseling, prenatal diagnosis, and screening	18
5.11.	Nutrition considerations and energy availability	18
5.12.	Medication and supplement considerations	19
5.13.	Additional medical considerations	20
6.	Research and community resources	20
7.	Knowledge gaps and future research directions	20
8.	Conclusion	22
	Disclosures	22
	Acknowledgments	22
	Appendix A. Supplementary Data	22
	References	22

1. Purpose

By the initiative of the Association for Glycogen Storage Disease (AGSD) in the United States, a national panel was organized to provide an educational resource that highlights current practices and approaches to the diagnosis and management of all clinical phenotypes of glycogen storage disease type IV (GSD IV), including the adult-onset form adult polyglucosan body disease (APBD). This guideline is not intended for the diagnosis or management of other disorders with polyglucosan accumulation.

2. General background

2.1. Overview

Glycogen serves as a storage form of glucose in humans and glycogen synthesis takes places 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) [1,2]. The first enzyme that initiates glycogen synthesis is the homodimer glycogenin which 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 the 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 [3]. In the setting of reduced GBE activity, glycogen synthesis is impaired; 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” which resembles plant amylopectin. Tight packing of the double-helices induces crystallization and renders the polyglucosan

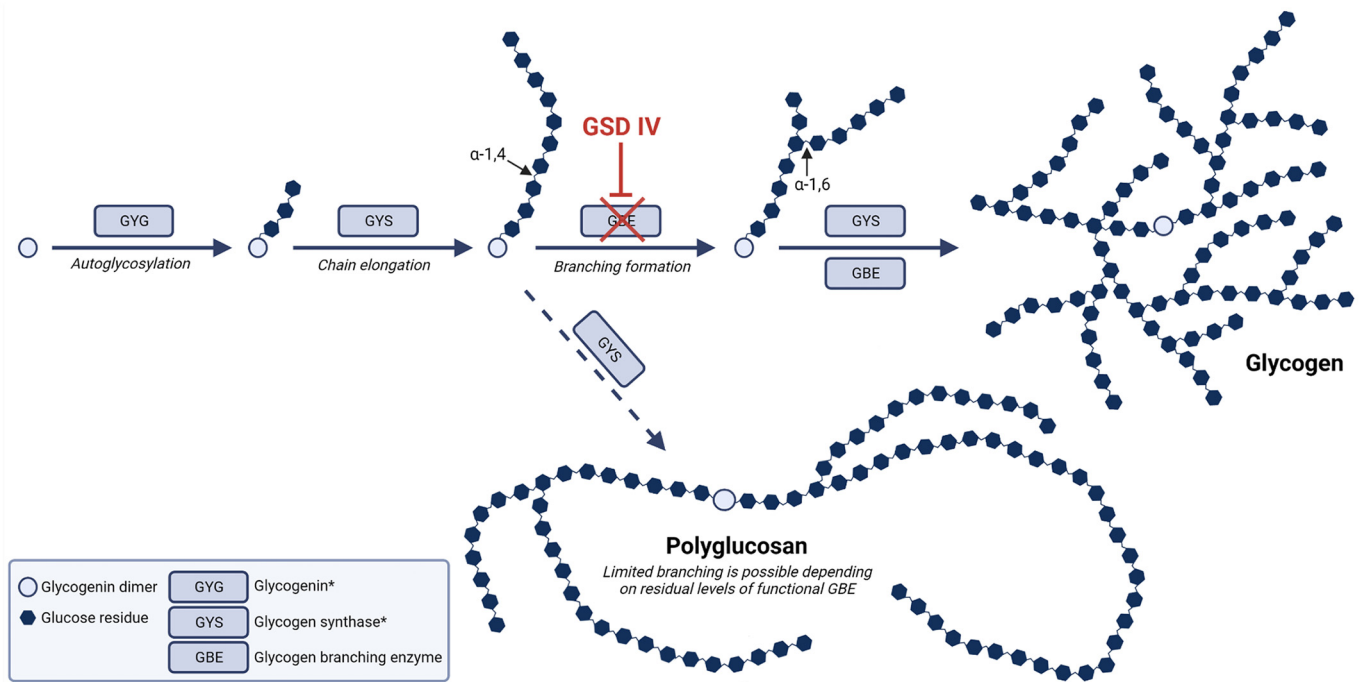


Fig. 1. Normal glycogen synthesis results in a spherical, highly branched polysaccharide compared to accumulation of polyglucosan in the setting of glycogen storage disease type IV (GSD IV). Polyglucosan accumulation occurs in all phenotypes of GSD IV, including the adult-onset form adult polyglucosan body disease (APBD). Enzymes involved in glycogen synthesis (glycogenin [GYG], glycogen synthase [GYS], and glycogen branching enzyme [GBE]) are indicated by shaded boxes. In normal glycogen synthesis (solid arrows), the homodimer glycogenin autoglycosylates and polymerizes the initial glucose residues, priming glycogen synthesis. GYS then acts as a glucosyltransferase and adds up to 10 glucose molecules to the glycogenin core via α -1,4 linkages, elongating the linear chain, and GBE transfers α -1,4-linked glucosyl units into an α -1,6 position, forming branches. GYS and GBE continue to work in balance to synthesize the spherical, branched glycogen structure ("Glycogen"). GSD IV is the result of deficiency of GBE activity, indicated by a red bar. In the setting of GSD IV, an alternative glycogen synthesis pathway occurs (dashed arrow) and GYS continues to elongate the glucosyl chain despite the lack of functional GBE, resulting in the formation of polyglucosan with long, linear outer chains. Limited branch points may be formed depending on residual levels of functional GBE. In this simplified visual, an example of polyglucosan with two branch points is shown.

* GYG and GYS each have two isoforms. *GYG1* is abundantly expressed in the heart and skeletal muscle, and *GYG2* is largely expressed in the liver. *GYS1* is abundantly expressed in the skeletal muscle and brain whereas *GYS2* is expressed in the liver.

water-insoluble [4,5]. Polyglucosan accumulates and aggregates in deposits referred to as "polyglucosan bodies" which disrupt cellular function. In the case of neurons, polyglucosan bodies disturb retrograde and anterograde axonal transport [6,7].

GSD IV is an ultra-rare autosomal recessive disease caused by biallelic pathogenic variants in the *glycogen branching enzyme 1* (*GBE1*) gene which results in reduced or deficient GBE activity. GSD IV has been reported in many different ethnic groups and is estimated to occur in 1 in 600,000 to 800,000 individuals worldwide (~3% of all GSD cases) [8]. The National Library of Medicine has recorded approximately 200 cases of the adult-onset form APBD worldwide [9]. APBD is of a particularly high frequency in the Ashkenazi Jewish population (carrier rate 1 in 48), and 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 background over age 50 years in the United States [10].

2.2. History

In the 1950s, Dorothy Hansine Andersen, a pediatrician and pathologist at Columbia University, first described a disease with familial cirrhosis and abnormal storage of glycogen in the liver [11,12], initially referred to as Andersen disease and later classified as GSD IV. Two additional cases were described in 1962 [13] and 1966 [14] which further revealed the presence of polysaccharide accumulation in tissues at autopsy. It was then confirmed by Brown and Brown that GSD IV is a result of GBE deficiency [15]. Over the following decades, the publication

of additional cases broadened the known range of clinical presentations associated with GBE deficiency to include patients with skeletal myopathy and/or cardiomyopathy during childhood [16–18] and adulthood [19], fatal neuromuscular weakness with congenital onset [20,21], and apparently "non-progressive" hepatic disease [22,23].

It was initially unclear whether APBD was an adult-onset form of GSD IV or a separate disease with different genetic cause. In 1980, several cases of "adult polyglucosan body disease" were formally described [7]. Shortly thereafter in 1981, Pellissier and colleagues described a "polysaccharide (amylopectin-like) storage myopathy" with impaired mobility and gait along with reduced leukocyte GBE activity [24]. In 1991, Lossos and colleagues documented that patients with APBD exhibit reduced GBE activity [25]. The term APBD was ultimately used to describe patients with reduced or deficient GBE activity and is now considered to be the adult-onset form of GSD IV.

2.3. Clinical variability

Clinically, GSD IV is characterized by a remarkable degree of phenotypic heterogeneity. Historically, a subtype system has been used to classify patients along the GSD IV spectrum based on their symptoms and presentations. This traditional subtype classification system includes: (1) fatal perinatal neuromuscular subtype, presenting in utero with fetal akinesia deformation sequence, decreased fetal movements, polyhydramnios, and fetal hydrops, with death typically in the neonatal period; (2) congenital/neonatal neuromuscular subtype, presenting in the neonatal period with profound hypotonia, respiratory distress, and dilated cardiomyopathy, with death typically in early infancy; (3) classic

(progressive) hepatic subtype, with rapid development of failure to thrive, hepatomegaly, splenomegaly, liver dysfunction, hypotonia, cardiomyopathy, and progressive liver cirrhosis, resulting in death from liver failure by age 3 to 5 years (without liver transplantation); (4) non-progressive hepatic subtype, presenting with hepatomegaly, liver dysfunction, myopathy, and hypotonia in early childhood, with variable cardiac, skeletal muscle, and neurologic involvement and survival without overt progression of liver disease as noted in the classic (progressive) hepatic subtype; (5) childhood/juvenile neuromuscular subtype, presenting with variable course ranging from onset in the second decade with a mild disease course to a more severe, progressive course resulting in death in the third decade; and (6) the adult-onset form, APBD [8,26]. APBD is considered a neurodegenerative disorder and most individuals present with progressive neurogenic bladder, gait difficulties (i.e., spasticity and weakness), sensory loss, autonomic dysfunction, and cognitive difficulties of varying severity; some affected individuals with APBD have less common phenotypes, including Alzheimer's disease-like dementia and axonal neuropathy, stroke-like episodes, and diaphragmatic failure [26]. APBD is also described to have a relatively predictable progression and natural history [27]; typically, the earliest manifestations are bladder dysfunction followed by gait disturbance that is a combination of spasticity with some peripheral nervous system (PNS) involvement, which leads to inability to walk. Survival is reduced with median survival in the mid-70s [27]; however, rate of disease progression can vary [28].

The use of this subtype system has been under scrutiny as many patients have clinical presentations that overlap across different subtypes categories [29], and the progression of GSD IV in childhood through adulthood remains unclear and underreported in the literature. A recent review of the literature highlighted the challenges and limitations of this subtype system [29]. Although some patients may present with phenotypes that are consistent with one of the aforementioned GSD IV subtypes, including APBD, others are challenging to account for under the established classification system. Notably, there are reports of several patients with GSD IV who presented with significant degrees of both hepatic and neurologic involvement, and others have been reported to exhibit phenotypes that are intermediate in severity between the established subtypes [29]. Altogether, this suggests that GSD IV is better conceptualized as a multidimensional clinical continuum, whereby hepatic, neurologic, and cardiac involvement occur to varying degrees.

Moreover, the spectrum of phenotypic variation associated with GBE deficiency has historically been divided into discrete clinical categories, whereby APBD has been recognized as a separate disorder rather than a part of the GSD IV clinical continuum, resulting in confusion among patients and clinicians. Despite all GSD IV phenotypes, including APBD, being caused by biallelic pathogenic variants in *GBE1*, there are two separate Online Mendelian Inheritance in Man (OMIM) entries: #232500 for GSD IV and #263570 for APBD, the latter referred to as “polyglucosan body neuropathy”. The distinction between GSD IV and APBD has been further challenged by reports of patients who presented with features of GSD IV during childhood and later developed APBD during adulthood [30]. Collectively, these findings highlight that the distinctions among the GSD IV subtypes and APBD should be regarded with caution as all phenotypes of GSD IV, including APBD, are caused by GBE deficiency.

3. Methods and process

3.1. Nomenclature GSD IV is also referred to as Andersen disease or Andersen glycogenosis. APBD is also referred to as adult-onset GSD IV, adult GSD 4, *GBE1*-APBD, or polyglucosan body neuropathy. GSD IV, including APBD, is also referred to as glycogenosis, brancher deficiency, brancher enzyme deficiency, branching enzyme deficiency, polyglucosan storage myopathy, polyglucosan body disease, amylopectinosis, GSD type 4, or GSD 4.

Herein, we have considered GSD IV to be a continuum of disease spectrum varying by age of onset, organ involvement, and severity.

Historically, APBD has been recognized as separate from the GSD IV clinical continuum. Yet, all phenotypes of GSD IV, including APBD, are caused by reduced/deficient GBE activity and therefore, unless otherwise stated, recommendations are applicable to all individuals affected by GSD IV, including APBD.

3.2. Consensus development panel

In collaboration with the AGSD 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” which included 19 specialists with expertise in medical genetics, diagnostics, hepatology, neurology, physical rehabilitation, cardiology, urology, genetic counseling, psychology, and dietetics. Based on expertise and clinical experience, each panelist was assigned a discipline section for consensus development. Panelists independently reviewed the current evidence base of GSD IV, including APBD, for (a) clinical and laboratory diagnosis, (b) treatment and management of hepatic, neurologic, muscular, and cardiac manifestations, (c) supportive and rehabilitative care, (d) general medical care, and (e) genetic aspects. A series of virtual meetings occurred between January to November 2022 in which panelists presented their recommended care standards, highlighted existing knowledge gaps, and facilitated discussions related to care practices for GSD IV that are inconsistent or not addressed in the literature. Each panelist drafted their recommended care guidelines and best practices for management of patients with GSD IV, including APBD. Consensus was defined as agreement among all panelists and was obtained for all sections. All panelists reviewed and approved the final guidelines. Recommendations are considered expert opinion.

3.3. Target audience

This guideline is directed at a wide range of care providers as GSD IV, including APBD, is nuanced, with variability in affected tissue systems including hepatic, cardiac, muscular, central nervous system (CNS), and PNS involvement. Although care is commonly provided by specialists in medical genetics, hepatology, neurology, physical medicine and rehabilitation, urology, and cardiology, it is important that primary care providers and other specialists involved in the care of individuals with GSD IV also be able to recognize the early symptoms, facilitate the diagnosis, and provide appropriate care. Therefore, these guidelines were developed to support clinicians and care providers across the continuum of care and patient lifespans.

4. Diagnosis

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

4.1. Differential diagnosis

Given the heterogeneous presentation of GSD IV, the differential diagnosis will vary based on the patient's age (pediatric versus adult) and predominant disease manifestations (hepatic, neurologic, muscular, and/or cardiac) (Table 1).

In general, GSD IV should be suspected in patients who have severe hepatomegaly with or without prominent splenomegaly in the first few months of life. The differential diagnosis for GSD IV with predominantly hepatic involvement includes conditions that are associated with progressive liver dysfunction and hepatomegaly in infancy or early

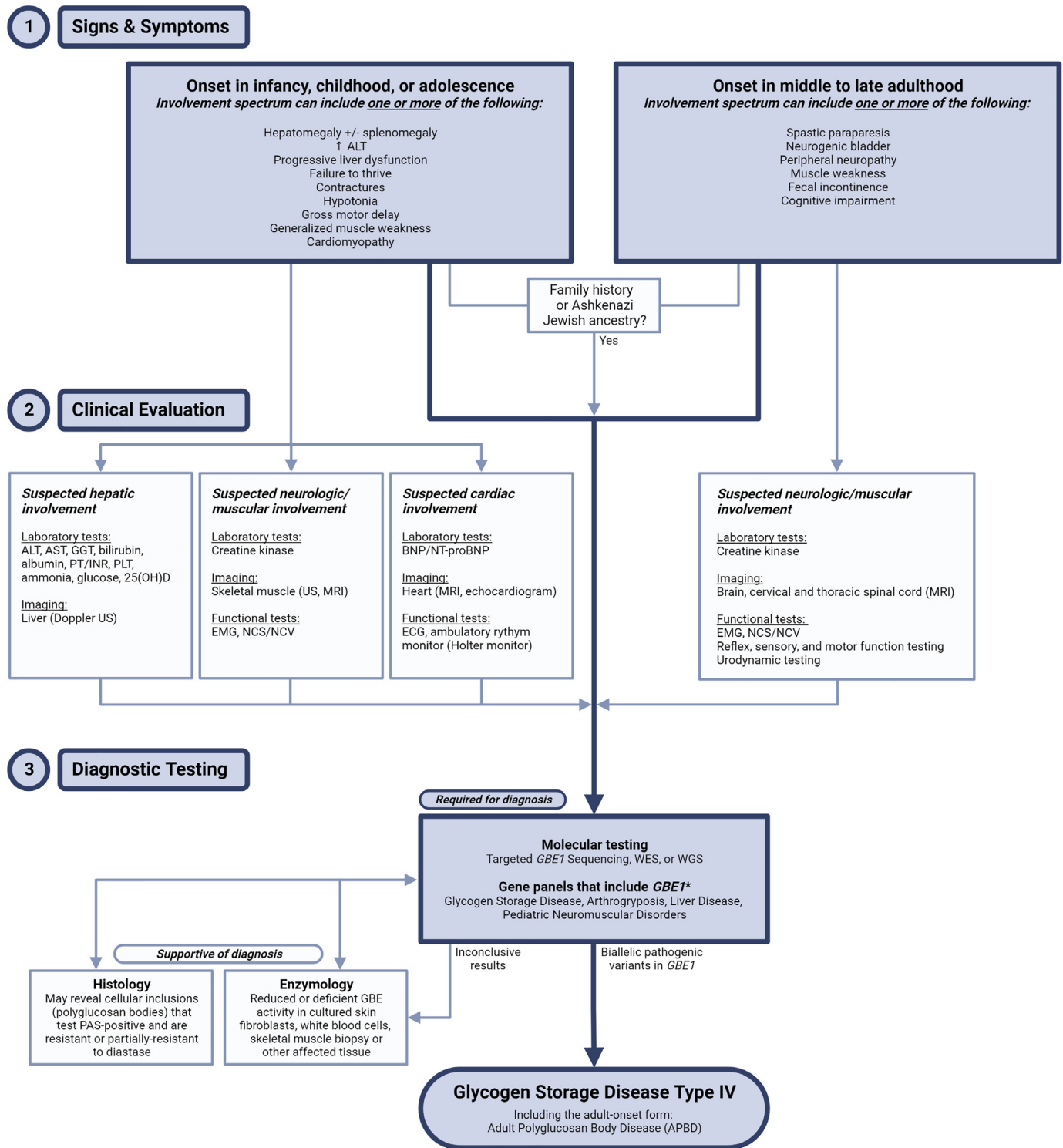


Fig. 2. A decision path to diagnose glycogen storage disease type IV (GSD IV), including adult polyglucosan body disease (APBD). The typical path to diagnosis is indicated with dark shaded boxes and arrows. Additional paths to diagnosis are indicated with light shaded boxes and arrows. The signs and symptoms of GSD IV, including APBD, are features that often overlap with other disorders which can result in delays in diagnosis and/or misdiagnosis, and therefore it is critical to follow the decision path to confirm a GSD IV diagnosis. The differential diagnosis will vary based on the patient's age and predominant disease manifestations (hepatic, neurologic, muscular, and/or cardiac). Clinical evaluation will be dependent on age of onset and suspected tissue system involvement.

* The list of genes included on gene panels are company-specific. Prior to selecting a gene panel, the ordering provider should ensure that *glycogen branching enzyme 1* (*GBE1*) is included on the panel.

Abbreviations: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), B-type natriuretic peptide (BNP), computed tomography (CT), creatine kinase (CK), electrocardiogram (ECG), electromyography (EMG), gamma-glutamyl transferase (GGT), glycogen branching enzyme (GBE), international normalized ratio (INR), magnetic resonance imaging (MRI), N-terminal-pro hormone BNP (NT-proBNP), nerve conduction study (NCS), nerve conduction velocity (NCV), platelet (PLT), prothrombin time (PT), ultrasound (US), whole exome sequencing (WES), whole genome sequencing (WGS), 25-hydroxy vitamin D (25(OH)D)

Table 1

Principal genetic disorders to differentiate from glycogen storage disease type IV (GSD IV), including the adult-onset form adult polyglucosan body disease (APBD).

Disorder	Gene	Overlapping features	Distinguishing features*
<i>A. Symptom onset in infancy or childhood with primarily hepatic involvement</i>			
GSD I (von Gierke disease) <i>Inheritance: AR</i>	G6PC, SLC37A4	Hepatomegaly, elevated ALT and AST early in disease course that usually improves with metabolic control	Nephromegaly, hypoglycemia, hyperlipidemia, lactic acidosis, hyperuricemia, large and numerous lipid vacuoles in hepatocytes
GSD III (Cori or Forbes disease) <i>Inheritance: AR</i>	AGL	Hepatomegaly, elevated ALT and AST, myopathy variable and progressive liver fibrosis	Hypoglycemia, hyperlipidemia, elevated CK, PAS-positive inclusions present in hepatocytes are sensitive to diastase
GSD VI (Hers disease) <i>Inheritance: AR</i>	PYGL	Hepatomegaly, elevated ALT and AST, variable and progressive liver fibrosis	Ketotic hypoglycemia, hyperlipidemia, PAS-positive inclusions present in hepatocytes are sensitive to diastase
GSD IX <i>Inheritance: AR, XL</i>	PHKA2 (type α2) PHKB (type β) PHKG2 (type γ2)	Hepatomegaly, elevated ALT and AST, ± myopathy (type β only), variable and progressive liver fibrosis	Ketotic hypoglycemia, hyperlipidemia, PAS-positive inclusions present in hepatocytes are sensitive to diastase
Mitochondrial hepatopathies <i>Inheritance: AR, AD, MT</i>	SCO1, BCS1L, POLG, DGUOK, MPV17, and more	Hepatomegaly, elevated ALT and AST, ± hypotonia	Hyperammonemia, hypoglycemia, lactic acidosis, cholestasis, steatosis
Congenital disorders of glycosylation <i>Inheritance: AR, XL</i>	MPI, TMEM199, CCDC115, ATP6AP1, and more	Hepatomegaly, elevated ALT and AST, hypotonia	Microcephaly, seizures, stroke-like episodes, altered TfIEF pattern
Hereditary fructose intolerance <i>Inheritance: AR</i>	ALDOB	Hepatomegaly, elevated ALT and AST	Triggered by acute ingestion of fructose, oral aversion for fructose-containing food, ± hypoglycemia
Fructose 1,6-biphosphatase deficiency <i>Inheritance: AR</i>	FBP1	Hepatomegaly, hypotonia	Ketotic hypoglycemia, lactic acidosis
Alpha-1 antitrypsin deficiency <i>Inheritance: ACD</i>	SERPINA1	Elevated ALT and AST, ± hepatomegaly, ± cirrhosis, PAS-positive diastase-resistant inclusions present in hepatocytes	Neonatal cholestasis, low serum alpha-1 antitrypsin level, necrotizing panniculitis, ± chronic obstructive lung disease
Transaldolase deficiency <i>Inheritance: AR</i>	TALDO1	Hepatomegaly, elevated ALT and AST	Neonatal cholestasis, intrauterine growth restriction, dysmorphic facial features, loose and wrinkly skin, renal dysfunction
Acid sphingomyelinase deficiency (Niemann-Pick disease types A and B) <i>Inheritance: AR</i>	SMPD1	Hepatomegaly, elevated ALT and AST	Deterioration of pulmonary function, diminished DLCO on PFT, atherogenic lipid profile, large and vacuolated foam cells on bone marrow biopsy, accumulation of lyso-sphingomyelin
Niemann-Pick disease type C <i>Inheritance: AR</i>	NPC1, NPC2	Hepatosplenomegaly, elevated ALT and AST, hypotonia	Developmental delay, cognitive impairment, hearing loss, ± infiltration of lungs with foam cells
Gaucher disease <i>Inheritance: AR</i>	GBA	Hepatosplenomegaly, thrombocytopenia	Bone manifestations including lytic lesions and osteonecrosis, increased lyso-Gb1 and chitotriosidase levels, progressive myoclonic epilepsy and other neurological findings (neuronopathic forms only)
Zellweger spectrum disorder <i>Inheritance: AR</i>	>10 genes	Hepatomegaly, elevated ALT and AST, ± cholestasis	Hearing loss, vision impairment, rhizomelic chondrodysplasia punctata
<i>B. Symptom onset in infancy or childhood with primarily neurologic, muscular, AND/OR cardiac involvement</i>			
Spinal muscular atrophy <i>Inheritance: AR</i>	SMN1	Congenital hypotonia, pulmonary compromise, fetal hypokinesia	Fasciculations, scoliosis, recurrent lower respiratory tract infections
GSD II (Pompe disease) <i>Inheritance: AR</i>	GAA	Cardiomyopathy, generalized hypotonia, respiratory distress	Marked cardiomegaly on chest X-ray, characteristic ECG findings including shortened PR interval, an increased QTc, and large LV voltages (No principle differentiating feature)
GSD XV (polyglucosan body myopathy type 2) <i>Inheritance: AR</i>	GYG1	Cardiomyopathy, proximal muscle weakness, polyglucosan bodies present in skeletal muscle and/or cardiac tissue	(No principle differentiating feature)
Polyglucosan body myopathy 1 <i>Inheritance: AR</i>	RBCK1	Cardiomyopathy, proximal muscle weakness, polyglucosan bodies present in skeletal muscle and cardiac tissue	(No principle differentiating feature)
PRKAG2 syndrome <i>Inheritance: AD</i>	PRKAG2	Myopathy, cardiomyopathy, polyglucosan bodies present in cardiac tissue	Characteristic ECG findings including ventricular pre-excitation with short PR interval and delta waves
Danon disease <i>Inheritance: XL</i>	LAMP2	Myopathy, cardiomyopathy, polyglucosan bodies present in CNS, cardiac, and skeletal muscle tissue	Intellectual disability, lysosomal glycogen accumulation on histology
Congenital disorders of glycosylation <i>Inheritance: AR, XL</i>	PMM2, ALG6, DOLK, and more	Hypotonia, cardiomyopathy	Seizures, eye disease, stroke-like episodes, altered TfIEF pattern
Mitochondrial encephalomyopathies <i>Inheritance: AR, XL, MT</i>	TAZ, NDUFS4, SDHA, BCS1L, SURF1, ATPAF2, DLD, PDHA1, mtDNA, and more	Muscle weakness or exercise intolerance, cardiomyopathy	Dementia, stroke-like episodes, seizures, lactic acidosis, characteristic findings on MRI
<i>C. Symptom onset in middle to late adulthood with primarily neurologic involvement</i>			
Adrenomyeloneuropathy <i>Inheritance: XL</i>	ABCD1	Cognitive and/or vision impairment, leg weakness/spasticity, sphincter disturbances, sexual dysfunction (males)	Elevated very long-chain fatty acids
Adult-onset Alexander disease <i>Inheritance: AD</i>	GFAP	Spastic gait, bladder incontinence, atrophy of cervical spinal cord on MRI	Characteristic Rosenthal fibers on histology
Hereditary spastic paraplegia <i>Inheritance: AR, AD, XL, MT</i>	>30 genes	Leg weakness/spasticity, sensory polyneuropathy	(No principle differentiating feature, dependent on type of hereditary spastic paraplegia)

For each disorder, the causative gene, inheritance pattern, overlapping features, and distinguishing features unique to that disorder are indicated. Conditions are separated by symptom onset and tissue involvement. This table was adapted from *GeneReviews*® [8,26].

Abbreviations: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), autosomal dominant (AD), autosomal codominant (ACD), autosomal recessive (AR), carbohydrate (CHO), creatine kinase (CK), central nervous system (CNS), diffusing capacity of the lungs for carbon monoxide (DLCO), electrocardiogram (ECG), glycogen storage disease (GSD), left ventricular (LV), glucosylsphingosine (lyso-Gb1), magnetic resonance imaging (MRI), maternally-transmitted mitochondrial DNA (MT), mitochondrial DNA (mtDNA), periodic acid-Schiff (PAS), pulmonary function test (PFT), QT dispersion (QTd), transferrin isoelectric focusing (TfIEF), X-linked (XL).

* Hypoglycemia with or without elevated ketones is not considered a typical feature of GSD IV, but has been observed in patients with GSD IV. Therefore, it should not be used as the principle differential diagnostic criteria.

childhood. Liver disease related to infectious etiologies, infiltrating disease (lymphoma, leukemia, histiocytosis), neoplasms (hepatoblastoma, vascular tumors), cystic fibrosis, progressive familial intrahepatic cholestasis, congenital hepatic fibrosis (cystic liver diseases), Mauriac syndrome in type 1 diabetes mellitus, ingestion of toxic substances or medical overdoses, and auto-immune diseases or viral hepatitis should be considered, as well as conditions that can cause acute liver failure including, but not limited to, tyrosinemia, galactosemia, citrin deficiency, viral hepatitis, urea cycle defects, hemophagocytic lymphohistiocytosis, and bile acid synthesis defect (5 β -reductase deficiency). GSD IV is not associated with severe hypoglycemia, steatosis, lactic acidosis, or hyperuricemia which are common in other GSD types and inborn errors of metabolism. Key diagnoses to consider include GSD types I (von Gierke disease), III (Cori or Forbes disease), VI (Hers disease), and IX, mitochondrial hepatopathies, congenital disorders of glycosylation involving liver disease, hereditary fructose intolerance, fructose 1,6-biphosphatase deficiency, alpha-1 antitrypsin deficiency, transaldolase deficiency, acid sphingomyelinase deficiency (Niemann-Pick disease types A and B), Niemann-Pick disease type C, Gaucher disease, and Zellweger spectrum disorder (Table 1A).

GSD IV should be suspected in any infant, child, or adolescent who presents with progressive generalized hypotonia, proximal and/or distal weakness, contractures/arthrogryposis, or unexplained cardiomyopathy. Principal differential genetic diagnoses will include spinal muscular atrophy, GSD II (Pompe disease), congenital disorders of glycosylation with myopathy and/or neurological disease, and mitochondrial myopathies (Table 1B). Additional differential diagnoses that can be ruled out with genetic testing include congenital and limb-girdle muscular dystrophies. It is also critical to differentiate GSD IV from conditions that are associated with polyglucosan inclusions in nervous, skeletal muscle, and/or cardiac tissue: GSD types VII (Tarui disease) and XV (polyglucosan body myopathy type 2), RBCK1 deficiency (polyglucosan body myopathy 1), PRKAG2 syndrome, Danon disease, and Lafora disease. Lastly, cerebral palsy is a multifactorial condition that is associated with spasticity, ataxia, hypotonia, and gross motor delay in childhood or adolescence.

APBD should be suspected in any adult patient who presents with neurogenic bladder and spastic paraparesis, with or without peripheral neuropathy. Conditions related to acquired nutritional deficiencies, hydrocephalus, infectious etiologies, infiltrating disease (neurosarcoidosis, multiple sclerosis [MS]), paraneoplastic disorders, and ingestion of toxic substances or medical overdoses should be considered [31]. A lumbar puncture can be performed to rule out inflammatory causes. In men with early urinary symptoms, benign prostatic hyperplasia should be ruled out. For individuals who present with symptoms consistent with APBD, neuroimaging (i.e., magnetic resonance imaging, MRI) is indicated to detect a selective pattern of CNS atrophy and any white matter changes. In individuals with APBD, MRI may show increased T₂*-weighted signal in the periventricular white matter, medulla, and pons, and in virtually all cases, medullary and cervical spinal cord atrophy [27,32]. Although white matter lesions on MRI along with sensory disturbance and lower limb spasticity are typical for MS, white matter lesions in APBD typically do not enhance with gadolinium [33]. Normal pressure hydrocephalus (NPH) syndrome has a clinical triad encompassing gait disturbance, urinary incontinence, and cognitive dysfunction [34], all of which are observed in APBD, and therefore should be ruled out. Principal differential genetic diagnoses include X-

linked adrenomyeloneuropathy, adult-onset Alexander disease, and hereditary spastic paraplegia (Table 1C). Additional differential genetic diagnoses include Parkinson's disease, vascular leukoencephalopathies (e.g., CADASIL, including *NOTCH3* and *HTRA1* disorders, and *COL4A1* and *COL4A2*-related disorders), some forms of Charcot-Marie Tooth disease, adult-onset metachromatic leukodystrophy, and amyotrophic lateral sclerosis (ALS); however, these disorders usually do not have concurrent spastic paraparesis and peripheral neuropathy which is typical of APBD. Corpora amylacea is the accumulation of polyglucosan in hyaline bodies and occurs in various tissues, including the brain, during natural aging and some neurodegenerative diseases.

A study conducted on a cohort of 30 patients with APBD found that all patients were initially misdiagnosed, likely due to lack of awareness of the clinical and imaging features characteristic of APBD [32]. The most common misdiagnoses were MS, ALS, cerebral small vessel ischemic disease, benign prostatic hyperplasia, and peripheral neuropathy, resulting in patients receiving inappropriate therapy, such as MS disease-modifying agents, immunosuppressive therapy, and antiplatelet agents to prevent stroke. The average diagnostic delay was 6.8 ($\pm$ 4.8) years. A formal study evaluating the rate of misdiagnosis or diagnostic delay in children or adolescents with GSD IV has not been reported. In general, misdiagnosis of GSD IV, including APBD, is likely to decrease with increased access to genetic testing via gene panels, whole exome sequencing (WES), and whole genome sequencing (WGS), yet the diagnosis can still be missed even with genetic testing (see Section 4.4). The current high occurrence of misdiagnosis and likelihood of underdiagnosis limits our understanding of disease prevalence and manifestations; comprehensive natural history studies are needed.

4.2. Clinical evaluation

The clinical evaluation of patients with GSD IV should be undertaken as a multidisciplinary approach with the aim of assessing the extent of disease expression across multiple systems. GSD IV is characterized by a remarkable degree of phenotypic heterogeneity, both with respect to the pattern of affected organs and the severity of clinical manifestations. Even within the neuromuscular spectrum of GSD IV, patients can present with neuromuscular dysfunction in utero, in early childhood, or even in middle to late adulthood, as is the case in APBD. Although this disorder has traditionally been divided into discrete hepatic and neuromuscular subtypes, many patients with GSD IV exhibit multisystem involvement with varying degrees of hepatic, cardiac, neurologic, and/or skeletal muscle disease [29]. Hence, even patients presenting with predominant involvement in one of these systems should be evaluated closely by specialists from multiple disciplines.

Although the workup of each patient should be tailored to his or her individual clinical presentation, the evaluation of a patient with GSD IV, including APBD, should include, at a minimum, several core elements: a comprehensive physical examination, routine imaging, and laboratory testing. In addition to comprehensive evaluation at baseline, patients with GSD IV should be followed longitudinally to monitor for progression of known disease manifestations and the onset of new symptoms. Notably, several patients with GSD IV diagnosed in childhood or adolescence have been reported to develop new disease manifestations – such as hepatocellular carcinoma (HCC) and cardiomyopathy – well into adulthood, decades after the initial onset of symptoms [30,35,36].

There have also been reports of patients initially presenting in early childhood with hepatomegaly and elevated aminotransferases, along with liver histopathology consistent with GSD IV, and despite the hepatopathy “spontaneously resolving,” they later presented in adulthood with neurological dysfunction consistent with APBD [30,33].

Therefore, longitudinal surveillance of patients with GSD IV, including APBD, should continue throughout the lifespan, ideally under the care of a multidisciplinary team composed of a metabolic disease specialist/biochemical geneticist and specialists dictated by the disease manifestations (Section 5).

4.3. Laboratory evaluation

A unique pattern of laboratory abnormalities for patients with GSD IV has not been recognized to date, and values are expected to differ based on the extent of tissue involvement in individual patients.

In patients with hepatic involvement, suggestive findings include elevated serum aminotransferases and mild hyperlipidemia [8,37]. Biochemical markers typical of other hepatic GSDs, such as lactic acidosis and hyperuricemia, are not commonly observed. The severe end of the disease spectrum of hepatic presentation includes progressive hepatosplenomegaly, portal hypertension, thrombocytopenia, variceal bleeding, ascites, hyperammonemia, along with persistent increase of aminotransferases, marked coagulopathy, cholestasis and hyperbilirubinemia, and worsening liver synthetic function with subsequent progression to liver failure [38,39]. It is possible for patients with hepatic GSD IV to remain relatively stable for an extended period of time even with definite portal hypertension. In the less severe forms of GSD IV with hepatic involvement, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) levels show elevations and are usually under 1,000 U/L [40–45]; the increase of aminotransferases does not progressively worsen over time and the synthetic function of the liver is preserved in many cases [40–45]. Progression of cirrhosis can be monitored by platelet count as used in the other chronic end-stage liver diseases. From general observation in pediatric patients with decompensated cirrhosis (end-stage liver disease), lower platelet count often reflects the severity of portal hypertension, with platelet count below 150,000/ μ L indicating mild portal hypertension and a platelet count below 100,000/ μ L indicating moderate to severe portal hypertension [46]; based on clinical observation, this trend is applicable to cases with GSD IV. Liver failure is associated with hyperammonemia, reduced 25-hydroxy vitamin D levels, and hypoglycemia due to impaired liver function (see Section 5.11). Elevated α -fetoprotein (AFP) has been noted in two cases, likely reflecting chronic liver injury and remodeling [47,48]. Most patients with APBD have normal aminotransferases and liver function.

Individuals with more marked neuromuscular involvement may exhibit mildly increased creatine kinase (CK) levels. Assessment of the true frequency and severity of CK elevations is difficult, as many reports do not report the exact timing of measurement in the neonatal period; CK levels are frequently elevated in unaffected infants during the first days of life. While CK level is not thoroughly reported, several case reports documented CK levels to be significantly elevated in the severe and lethal neuromuscular form [20,49–65], as well as in the less severe neuromuscular form [66] and APBD [19,24,33,67–70]. Moreover, CK elevations are under-reported in patients with adult-onset cardiomyopathy while blood B-type natriuretic peptide (BNP) or N-terminal-pro hormone BNP (NT-proBNP) are increased in most cases with severe cardiac presentation [54,71,72]. Patients with APBD and marked neurologic involvement may show unspecific findings in cerebrospinal fluid (elevated glucose or protein).

4.4. Diagnostic testing

4.4.1. Molecular genetic analysis

All GSD IV presentations, including APBD, are caused by variants in *GBE1*. Diagnosis of GSD IV is confirmed by the presence of two

pathogenic disease-causing variants in the *GBE1* gene in an individual. *GBE1* is located on chromosome 3p12.2 (GRCh38.p14) and is the only known gene associated with GSD IV, including APBD [8,26]. *GBE1* has a coding sequence consisting of 2,106 base pairs with 16 exons encoding a 702-amino acid GBE protein translated as a single polypeptide [73]. GBE protein has both N- and C- terminus highly conserved domains with sequence similarities to isoamylase and α -amylase, respectively [71]. A variety of *GBE1* variants and large gene deletions have been known to cause GBE enzyme reduction or deficiency. The large number of pathogenic variants in *GBE1* signify the underlying disease heterogeneity and a need for pursuing large deletion/duplication analyses for GSD IV. Exon 12 has been reported to be a variant hotspot [73]. The c.986A>C (p.Tyr329Ser) variant on exon 7 is common in the Ashkenazi Jewish population (estimated carrier rate 1 in 48 [10]) either in a homozygous state or compound heterozygous with an intronic variant IVS15 +5289_5297delGTGTGGTGGinsTGTTTTTACATGACAGGT [74,75].

Molecular testing can be performed as single gene testing through Sanger sequencing combined with deletion/duplication analysis if the clinical phenotype is compelling for GBE deficiency. *GBE1* sequencing alone detects ~74% of the pathogenic and likely pathogenic variants; if combined with deletion/duplication analysis, the detection rate increases to ~85% [8]. To date, there are 128 pathogenic or likely pathogenic variants reported in the *GBE1* gene known to cause GSD IV in The Human Gene Mutation Database (HGMD) (<http://www.hgmd.cf.ac.uk/ac/gene.php?gene=GBE1>). A large number of disease-causing variants scattered throughout the *GBE1* gene have been identified; these include missense (~50% of the pathogenic variants), nonsense, splice site, small frameshift deletions and insertions, and large gene deletions and duplications. There are over 150 variants of uncertain significance (VUS) and 37 variants with conflicting interpretations reported in the *GBE1* gene (obtained from ClinVar database <http://www.ncbi.nlm.nih.gov/clinvar>, accessed November 1, 2022) which could hinder a confirmatory diagnosis of GSD IV for many patients. The molecular basis of tissue-specific GBE activity in patients with GSD IV is not yet clearly understood and there are no clear genotype-phenotype correlations available at this time. In general, a combination of two null variants (nonsense, frameshift deletions, truncating and large deletion variants) typically produces the severe neuromuscular phenotypes [8], while the combination of one null and one missense variant or two missense variants has been reported to produce a variety of hepatic and neuromuscular phenotypes.

If the clinical phenotype is broad and not distinctive from other GSDs or other inherited metabolic disorders, WES, WGS, or a multigene panel targeting liver, muscle, neurological, or heart diseases (panel choice dependent on suspected tissue involvement) may be a better option for diagnosis. One needs to make sure that the genes in the panel include the gene of interest (*GBE1*) and that the diagnostic coverage for each gene is reasonable so that pathogenic variants are not missed. Comprehensive next-generation sequencing (NGS) including WES, exome array, and WGS can also be performed depending upon the clinical presentation and disease phenotype. Depending on the company performing the genetic testing, results may report *GBE1* as being associated with “GSD IV,” and others as “APBD” only. It is important for the ordering provider to recognize that APBD is a phenotype of GSD IV, and all phenotypes of GSD IV are caused by two pathogenic variants in *GBE1*. There have been continuous improvements made in massively parallel sequencing (gene panels, WES and WGS) and sophisticated bioinformatics tools are being applied for data analysis; however, due to wide availability of NGS, a large number of VUS are being discovered in *GBE1* as well. Thus, molecular confirmatory diagnosis of GSD IV at times can be elusive due to the presence of VUS and/or lack of two pathogenic or likely pathogenic alleles in *GBE1*. Additionally, the presence of intronic variants or large exon/multi-exon gene deletions need to be investigated through deletion/duplication testing and/or gene expression analysis through RNA-Seq or other modalities [75]. Therefore, if genetic testing reveals only one pathogenic variant in *GBE1* and the clinical phenotype is consistent with GSD IV, additional molecular testing is warranted [76].

4.4.2. Biochemical analysis

Historically, measurement of functional GBE activity was critical for diagnosis when molecular genetic testing was not widely available. With increased access to genetic testing, the need for enzymology is not required in cases that have two documented pathogenic variants in *GBE1*. For cases that have inconclusive genetic testing results or require further confirmation, a diagnosis of GSD IV is supported by the indication of deficient or reduced functional GBE activity in cultured skin fibroblasts, white blood cells, heart, skeletal muscle, liver, and peripheral nerve biopsy tissues based on the clinical symptoms. Biopsy tissue should be snap frozen and transported to the diagnostic laboratory frozen as enzyme activity could be compromised if biopsy tissue is exposed to higher temperatures and thaws. Liver is not the preferred tissue for measuring GBE residual enzyme activity because of interference of other isozymes, such as amylase activity, with branching enzyme activity measurement, thus giving equivocal activity levels. Moreover, if there is extensive liver fibrosis or cirrhosis, GBE enzyme activity is considered compromised and enzyme testing may yield false positive results. Measuring GBE activity in tissues is nuanced, and therefore, enzymology testing should be conducted at a laboratory experienced with analyzing tissue from patients with GSD IV. GBE activity in tissues from individuals affected by GSD IV, including APBD, usually ranges from 0 to 30% of normal control. However, GBE activity levels can vary in different tissue types [16,77,78]; therefore, measuring GBE activity alone may not be a good predictor of the clinical course or the severity of the disease phenotype in any individual. Moreover, the diagnosis can be missed if GBE activity is not measured in an affected tissue, as tissue GBE levels can be normal in one tissue and reduced or deficient in another [79]. Rarely, GBE activity may be secondarily reduced due to alternative disorders, including C2orf69 deficiency which is associated with deficient GBE activity in the liver [80].

The glycogen content can be mildly elevated in affected tissues (liver, skeletal muscle, heart), and the glycogen can be abnormal in structure (longer outer branches; indicated by the glucose-1-phosphate to glucose ratio). Western blot analysis can also be performed on a research basis to prove the absence of GBE protein in erythrocytes, leukocytes, lymphoblastoid cells, and skin fibroblast cells, but this testing is not currently clinically available.

4.4.3. Histopathology

Due to deficiency or reduction in GBE activity, accumulated glycogen (polyglucosan) has fewer branch points with longer linear, non-branched outer chains that gives an amylopectin-like appearance. Polyglucosan is resistant to diastase (amylase) digestion, whereas normal branched glycogen is not, and therefore, polyglucosan can be visualized by staining the tissue with periodic acid-Schiff (PAS) and diastase (amylase). Histopathology of affected tissues typically shows PAS staining for storage material, which is resistant or partially resistant to diastase digestion. However, the presence of PAS-positive diastase-resistant storage material is not sufficient for a GSD IV diagnosis. Polyglucosan can accumulate in tissue as a result of various disorders, including GSD types VII (Tarui disease) and XV (polyglucosan body myopathy type 2), RBCK1 deficiency (polyglucosan body myopathy 1), PRKAG2 syndrome, Danon disease, and Lafora disease, and can also occur in healthy older persons (corpora amylacea). In alpha-1 antitrypsin deficiency, misfolded, polymerized proteins can accumulate in the hepatocytes and stain as PAS-positive diastase-resistant. Moreover, the amount of polyglucosan that is able to be visualized on histology slides is dependent on the amount of time the diastase is left to digest the tissue. Therefore, histopathology should be conducted at a laboratory experienced with analyzing tissue from patients with GSD IV. Lastly, the level and accumulation of polyglucosan deposition in GSD IV is variable, and therefore it is possible for a biopsy to not reflect the individual patient's disease pathology. This has occurred in situations where pediatric patients with GSD IV presenting with hepatic involvement did not have polyglucosan in their skeletal muscle biopsy

[81,82], and vice versa where patients with predominant neuromuscular involvement did not have polyglucosan bodies in their liver biopsy [83,84]. Similarly, there are cases where symptomatic APBD patients diagnosed via genetic testing and/or enzymology had a skeletal muscle biopsy that did not show the presence of polyglucosan [74,85]. This highlights the need for proper selection of tissue for biopsy if histopathology is desired to support a GSD IV diagnosis.

For those with symptoms of hepatic involvement (i.e., hepatomegaly and elevated ALT and AST), a liver biopsy is recommended to assess the extent of liver disease. The liver biopsy demonstrates polyglucosan accumulation in the cytoplasm of hepatocytes, often in association with a pattern of lobular fibrosis, distorted hepatic architecture with diffuse interstitial fibrosis, and wide fibrous septa surrounding micronodular areas of parenchyma [86–88]. The polyglucosan bodies can be seen in the macrophages as well, suggesting that ingested material is derived from the cytoplasmic inclusions [89]. Electron microscopic examination reveals characteristic fibrillar amorphous electron-dense inclusions within hepatocytes, which aids in the diagnosis of GSD IV [88,90]. The fibrosis pattern is heterogeneous and differs from the fibrosis pattern of typical cirrhosis due to chronic viral hepatitis. Moreover, the timing and progression of liver fibrosis in GSD IV is not well understood. Multiple patients with GSD IV have had marked bridging fibrosis or features suggestive of cirrhosis on their liver biopsy, but did not progress to overt liver failure or require liver transplantation. Thus, the histological finding of liver fibrosis should not be used to predict risk for development of liver failure.

For those with neurological manifestations (i.e., hypotonia, myopathy, weakness, gait abnormalities, peripheral neuropathy, or neurogenic bladder), biopsies of apocrine glands of axillary skin, skeletal muscle, or peripheral (sural) nerve can reveal polyglucosan inclusions in the cellular cytoplasm, with the exception of neurons which have intra-axonal polyglucosan bodies. In deceased patients with neurological manifestations of GSD IV, including APBD, autopsy of the brain and spinal cord typically reveals widespread polyglucosan accumulation in the astrocytes, and in some cases, microglia, oligodendrocytes, and/or neuronal processes [18,20,91–95]. For those with cardiac involvement (i.e., diagnosed cardiomyopathy), a myocardial biopsy often reveals the presence of polyglucosan bodies but has a limited role in cardiac management.

DIAGNOSTIC TESTING RECOMMENDATIONS

- *GBE1* harbors a large number of disease-causing variants (missense, nonsense, splicing, small deletions/duplication and large deletions/duplication) scattered throughout the gene.
- There are many private/family variants identified in *GBE1*.
- The pathogenic c.986A>C (p.Tyr329Ser) missense variant is common in the Ashkenazi Jewish population (estimated carrier rate 1 in 48).
- Diagnosis is confirmed by demonstrating presence of biallelic pathogenic or likely pathogenic variants in the *GBE1* gene. If genetic testing is inconclusive but there is clinical suspicion, additional molecular testing is warranted.
- If molecular testing is inconclusive, diagnosis is confirmed by demonstrating functional GBE enzyme reduction or deficiency in skin fibroblasts, liver, or skeletal muscle (tissue selected based on presenting symptoms). Given the nuance of GBE activity in tissues, enzymology testing should be conducted at a laboratory experienced with analyzing tissue from patients with GSD IV.
- Histopathology of tissues may reveal the presence of storage material (polyglucosan) which stains positive for PAS and is resistant or partially resistant to diastase (amylase) digestion. However, the presence of PAS-positive diastase-resistant storage material alone is not sufficient for a GSD IV diagnosis.
- Elevation of glycogen content in affected tissues with structural abnormality (longer outer branches of glycogen) is consistent with GSD IV, including APBD.

5. Medical management

GSD IV is a multisystem disorder with variable primary tissue manifestations ranging from hepatic, muscular, neurologic, and/or cardiac involvement. Affected individuals are best managed by a multidisciplinary team led by a physician with expertise in this disorder. Team

members should include a metabolic disease specialist/medical geneticist and specialists dictated by the disease manifestations (Tables 2 and 3). 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. Regardless of age at initial presentation or symptoms, multidisciplinary, longitudinal follow-up is warranted. The psychological and emotional impact of this disease on the patients, their families, and their caregivers should be considered.

5.1. Hepatology

5.1.1. Disease expression

Hepatic manifestations in GSD IV most commonly present in early childhood before age 5 years. Liver involvement in APBD is less common, with chronic liver disease being noted in one case of APBD [96] and liver metastases in another [91]. There are additional cases of APBD revealing polyglucosan accumulation in hepatocytes on autopsy, despite having minimal clinical liver involvement; given the lack of liver dysfunction, it appears these were incidental findings of widespread polyglucosan deposition.

Hepatomegaly is the most common initial presentation of hepatic GSD IV in children [71,97]. In most cases, patients with hepatic GSD IV are born without specific complications at the time and are considered healthy. Typically, patients with hepatic GSD IV develop hepatomegaly during the first few months of life, which is often first noticed by pediatricians or caregivers. The degree of hepatomegaly and liver dysfunction varies greatly among individual cases, ranging from minimal to severe. The pathophysiology of hepatomegaly is due to polyglucosan accumulation in hepatocytes. The mechanism of hepatocellular

Table 2

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	Provision of 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 and symptom onset in infancy, childhood, or adolescence should undergo comprehensive, multidisciplinary evaluations to assess for and manage hepatic, muscular, neurologic, and cardiac involvement.

Table 3

Disease characterization and recommended clinical surveillance for patients affected by the adult-onset form of glycogen storage disease type IV (GSD IV): 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 delay, decline, or psychiatric manifestations and provision of appropriate management techniques
Cardiology	Evaluate for presence, onset, and progression of cardiomyopathy
Nutrition	Provision of 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.

dysfunction associated with the accumulation of polyglucosan is likely multifactorial and yet to be determined. It is important to note that, in addition to hepatomegaly, some patients can also develop or present with splenomegaly. The liver and spleen are easily palpable and often manifest as a rocky surface texture. In most cases, the production of coagulation factors by the liver remains intact, and no complications from portal hypertension are evident in early infancy; cholestasis/jaundice is rarely seen. Moderate elevation of serum aminotransferases is often the only abnormal laboratory finding at the time of presentation. GSD IV can progress to severe portal hypertension and liver dysfunction in the first few years of life, requiring liver transplantation for long-term survival. In contrast to other types of GSD (i.e., types I, III, VI, and IX) where hypoglycemia is a presenting and predominant feature, hypoglycemia-related symptoms are typically absent. However, there are reports of some cases of patients with hepatic GSD IV that presented with hypoglycemia requiring nutritional supplementation to maintain blood glucose levels (see Section 5.11).

Historically, cases with severe liver dysfunction and death before age 3 to 5 years without liver transplantation were categorized as the “progressive” (or “classic”) type of hepatic GSD IV [8]. Cases with mild and/or resolved liver dysfunction were termed the “non-progressive” hepatic type [41,42,98,22,23]. This categorization is applied retrospectively and is considered outdated due to the variation in liver disease progression. Nonetheless, liver transplantation has been indicated previously based on the diagnosis of hepatic GSD IV alone without careful monitoring of the progression of liver dysfunction and portal hypertension (i.e., preemptive liver transplantation before the onset of clinically significant portal hypertension or decompensating cirrhosis). Therefore, the natural disease progression is unclear for some cases. For example, there are cases with hepatic GSD IV who have remained relatively stable for an extended period of time (beyond 5 years of age) even with definite portal hypertension, indicating that the progression rate may vary among patients. There are no specific clinical parameters for GSD IV during early infancy or childhood that help predict the liver disease course, and

currently, no genotype-phenotype correlation has been established for hepatic GSD IV [42,51]. Liver biopsies of patients with hepatic GSD IV often exhibit liver fibrosis; the extent of liver fibrosis does not predict the course of liver disease and cannot differentiate those who will require liver transplantation. There are cases of fibrosis on initial liver biopsy during childhood in patients who survived without liver transplantation for decades [23,41,42,98]. Therefore, the role of repeat surveillance liver biopsies is unclear. We recommend using the clinical signs of portal hypertension to assess the progression of liver disease as this better reflects the stage of cirrhosis and liver dysfunction.

Patients with the lethal neuromuscular phenotype at birth or shortly thereafter are thought not to have hepatosplenomegaly or liver dysfunction [59,99,100]. However, there are reported patients with severe neuromuscular involvement that had hepatic fibrosis on autopsy and/or elevated aminotransferases or hepatomegaly, as well as many patients with predominantly neuromuscular manifestations who later develop hepatic involvement [29]. Therefore, even if the initial symptoms are predominantly neuromuscular, referral to a hepatologist is warranted. It is important to note that, outside of environmental and lifestyle contributors, incidental aminotransferases elevations may be due to GSD IV even if the patient's symptoms are predominantly neuromuscular; in these situations, AST is typically higher than ALT due to muscle involvement.

There are reports of patients with hepatic GSD IV who had "resolution" of liver disease in childhood and later developed APBD in adulthood [30]. This highlights that pediatric-onset GSD IV and APBD are part of a clinical continuum and further suggests that all patients with GSD IV need lifelong monitoring. The link between hepatic GSD IV and progression to APBD, as noted in some cases, requires further investigation.

5.1.2. Evaluation and management

Since liver disease is not common in APBD, the following information is tailored for pediatric-onset GSD IV and, unless stated otherwise, typically not applicable to APBD. Rather, recommendations for evaluation and management of liver involvement in APBD are listed separately.

For pediatric-onset GSD IV, formal evaluation for liver involvement at the time of diagnosis and longitudinal follow-up is recommended. Imaging of the abdomen (Doppler ultrasound) is supportive of diagnosis, and for those with symptoms of hepatic involvement (i.e., hepatomegaly and elevated ALT and AST), a liver biopsy is recommended to assess the extent of liver disease. Careful monitoring of liver synthetic function, cholestasis, and the progression of portal hypertension is key to the management of liver disease due to GSD IV. Routine abdominal imaging including an ultrasound every 6 months and annual ultrasound-based elastography (i.e., FibroScan) or MRI-based elastography (magnetic resonance elastography; MRE) are indicated for monitoring the progression of cirrhosis. Laboratory tests including serum ALT, AST, GGT, bilirubin (direct and indirect), albumin, prothrombin time and international normalized ratio (PT/INR), platelet count, ammonia, glucose, and 25-hydroxy vitamin D should be evaluated every 3 to 6 months to monitor hepatic function, progression of portal hypertension, fat-soluble vitamin deficiencies, and cholestasis.

Given that liver disease can progress rapidly with decompensating cirrhosis and patients may require liver transplantation, it is recommended to refer all patients with hepatic GSD IV to a pediatric hepatologist and a liver transplantation center as soon as liver involvement is confirmed. Clinical signs of portal hypertension are indicative of advanced disease, yet it is possible for some patients to

remain relatively stable for an extended period of time even with definite portal hypertension. Therefore, the development of portal hypertension does not automatically warrant liver transplantation. It is recommended that all patients be closely monitored using standard clinical management for portal hypertension [101,102]. Monitoring the progression of liver disease and comorbidities of heart and/or muscle disease are critical to determine the indication for liver transplantation and the timing thereof. Once ascites develops, cirrhosis enters a decompensation process; thus, patients with hepatic GSD IV need liver transplantation evaluation by experts before the development of significant ascites. Due to the multisystemic nature of GSD IV, highly personalized care and management are crucial before and after liver transplantation. Refer to Section 5.3 for considerations and indications for liver transplantation.

An abdominal Doppler ultrasound is indicated when a physical exam reveals ascites or there is sudden, acute weight gain, primarily to evaluate portal vein flow to rule out thrombosis as the latter impacts the planning of liver transplantation. The development of ascites indicates decompensation of cirrhosis and it can be controlled by diuretics, including spironolactone. When ascites develops abruptly, diagnostic paracentesis is indicated to rule out spontaneous bacterial peritonitis. Long-term antibiotics can be given for prophylaxis of spontaneous bacterial peritonitis and small bowel bacterial overgrowth due to malabsorption and intestinal edema in the setting of compromised splenic function and neutropenia. Progression of liver dysfunction to liver failure results in coagulopathy, variceal bleeding, cholestasis, hepatic encephalopathy, growth failure, protein-energy malnourishment, and nutrient deficiencies (see Section 5.11 for nutrition considerations). Upper gastrointestinal endoscopy with banding of varices is indicated for patients that have evidence of gastrointestinal bleeding (melena); however, it is not recommended for surveillance of esophageal varices for pediatric patients without signs of bleeding. Variceal bleeding can cause acute decompensation and multi-organ failure. Standard clinical management, including endoscopic banding and sclerotherapy, is indicated. The safety and efficacy of octreotide for variceal bleeding have not been established; therefore, we recommend using octreotide with caution. Non-selective β -blockers can be used for secondary prophylaxis for variceal bleeding; however, cardiology should be consulted before starting β -blockers for patients who have cardiomyopathy, and particularly for cases of advanced liver disease, caution should be taken with β -blockers due to their potential to mask symptoms of hypoglycemia. Thrombocytopenia and neutropenia due to hypersplenism can be severe. Thrombocytopenia increases the risk of variceal bleeding. Neutropenia compromises the immune system, and prophylactic antibiotics are indicated when severe.

Along with monitoring for progression of portal hypertension, careful monitoring of liver function is indicated for all cases with hepatic GSD IV. Infants with GSD IV exhibit mild coagulopathy; however, synthetic dysfunction due to liver failure is rare until end-stage. Mild coagulopathy is more likely due to vitamin K deficiency from poor nutrition status, chronic diarrhea, and bacterial overgrowth of the small bowel. Jaundice/cholestasis also appear late in the disease stage. When cholestasis progresses, fat-soluble vitamins (A, D, E, and K) should be supplemented to prevent deficiencies (see Section 5.11). There are reports of hepatocellular adenomas (HCA) [72,103] and HCC in hepatic GSD IV [36,48], and therefore routine imaging and monitoring of AFP are warranted. Of note, in other types of GSD (I and III), AFP is not considered a reliable marker of HCA or malignant HCC transformation [104–107]. Management and treatment of individuals who develop HCA or HCC should be directed by the hepatologist with an approach tailored to the individual patient.

HEPATOLOGY RECOMMENDATIONS

Recommendations for pediatric-onset GSD IV:

- All patients, regardless of presenting symptoms, should receive hepatic evaluation at the time of diagnosis and longitudinal follow-up.
- Consider referral to a pediatric hepatologist and liver transplantation center as soon as diagnosis is confirmed. Monitoring the progression of liver disease and comorbidities of heart/neuromuscular disease are critical to determine the indication for liver transplantation and the timing thereof.
- An individualized approach is needed for consideration of liver transplantation. There is variation in liver disease progression in GSD IV and the extent of liver fibrosis on liver biopsy does not predict the course of liver disease, nor can it differentiate those who will require liver transplantation.
- Abdominal imaging of the liver and spleen by ultrasound every 6 months and annual liver elastography (FibroScan or MRE) are indicated for monitoring the progression of liver disease, including cirrhosis, portal hypertension, and tumor formation.
- Laboratory tests include serum ALT, AST, GGT, bilirubin (direct and indirect), albumin, PT/INR, platelet count, ammonia, glucose, and 25-hydroxy vitamin D every 3 to 6 months to monitor hepatic function, progression of portal hypertension, fat-soluble vitamin deficiencies, and cholestasis.
- Given the risk of HCC in hepatic GSD IV, periodical monitoring of AFP and routine abdominal imaging is recommended.
- In addition to routine surveillance, abdominal Doppler ultrasound is indicated if new ascites is identified on physical exam or if there is acute weight gain to address portal vein thrombosis as it impacts the planning of liver transplantation.
- When ascites develops abruptly, diagnostic paracentesis is indicated to rule out spontaneous bacterial peritonitis.
- Prophylactic antibiotics are indicated for small bowel bacterial overgrowth and spontaneous bacterial peritonitis in the setting of compromised splenic function and neutropenia.

Recommendations for APBD:

- Liver disease is not common, and formal hepatology evaluation upon diagnosis is not necessary.
- Laboratory tests include serum AST, ALT, GGT, bilirubin (direct and indirect), albumin, PT/INR, and platelet count every year to screen for liver dysfunction. If any of these tests are abnormal, refer the patient to a hepatologist.

5.2. Cardiology

5.2.1. Disease expression

Cardiac involvement has been noted in patients who have hepatic or neuromuscular involvement, or both [29], as well as in APBD [79]. Rarely, cardiac involvement has been noted as the sole disease manifestation (i.e., in the absence of additional neuromuscular or hepatic involvement) [29]. The cardiac manifestations of GSD IV, including APBD, typically reflect primary myocardial disease or cardiomyopathy, which can range from ventricular hypertrophy (hypertrophic cardiomyopathy, HCM) to ventricular dilation and loss of systolic function (non-ischemic dilated cardiomyopathy, DCM). While cardiomyopathy typically occurs in the context of other non-cardiac manifestations of disease, predominant cardiac involvement has been described [78,108]. The age of cardiac disease onset is variable, from severe, symptomatic disease in early childhood [71,109,110] to asymptomatic disease noted in adulthood [111,112]. The severity of disease progression is similarly variable, and can range from asymptomatic [113] to symptomatic heart failure requiring cardiac transplantation [114,115]. Isolated cases and limited case series have identified a range of possible electrical abnormalities or arrhythmias of the heart, including non-sustained VT, intraventricular conduction delay (bundle branch block), and atrioventricular conduction block requiring pacemaker implantation [18,78]. Further, cases of sudden death have been reported, although it remains unclear whether electrical abnormalities and arrhythmia predisposition can occur in the absence of significant cardiomyopathic disease [78,113,116].

5.2.2. Evaluation and management

For all patients with GSD IV, including APBD, cardiac evaluation at the time of diagnosis and longitudinal follow-up, ideally by a specialist in cardiomyopathy and cardiovascular genetics, is recommended. The initial

evaluation should involve a detailed personal history, family history, and physical exam. Testing that should be considered at the time of diagnosis includes baseline BNP or NT-proBNP, 12-lead ECG, ambulatory rhythm monitor (such as a Holter monitor), and cardiac MRI with contrast. If a cardiac MRI is not feasible, a transthoracic echocardiogram can be considered. Surveillance should be tailored to the individual patient, development of symptoms, and disease progression and should typically include an annual clinical evaluation, ECG, ambulatory rhythm monitor, and echocardiogram. Cardiac MRI with contrast should be repeated every 3 to 5 years, or earlier with clinical change. Looping event monitors, including subdermal implantable monitors, can be considered in the setting of symptoms concerning for cardiac arrhythmias such as sustained palpitations, suspected cardiogenic presyncope, or syncope. Repeat BNP/NT-proBNP can be considered with episodes of suspected cardiac insufficiency or heart failure. Myocardial biopsy has a limited role in cardiac management and can be considered in an institution and/or patient-specific manner. Similarly, cardiac catheterization may be considered, particularly to evaluate for elevated end-diastolic pressures; however, the decision should be individualized to the institution and/or patient.

There is limited data on medical therapies utilized to treat the cardiac manifestations of GSD IV, including APBD, and the current literature is heterogeneous. Existing consensus guidelines for the management of cardiomyopathies and heart failure in pediatric and adult patients can inform an overall management strategy, which individualizes approach based on whether the patient hosts a HCM or DCM subtype [117–120]. Management of individuals with GSD-associated cardiomyopathy should be performed in partnership with specialists in cardiomyopathy and/or heart failure. For asymptomatic individuals without evidence of cardiac disease, surveillance without cardiac medications is reasonable. For individuals with HCM, use of β 1-selective β -blockers, such as metoprolol, is reasonable. For individuals with DCM, use of either β -blockers (either β 1-selective, or combination non-selective β 1/ α 1 blocker, such as carvedilol), or either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), is reasonable. For advanced DCM, β -blockers can be combined with ACE inhibitors or ARBs at the discretion of the provider. Further, for symptomatic individuals with DCM, the use of diuretics is reasonable. Successful treatment of arrhythmias with β -blockers and sotalol have been reported; however, antiarrhythmic should be individualized to the specific patient in consultation with clinical electrophysiologists given the limited data available. For patients with significant liver disease and/or a history of hypoglycemia, caution should be taken when using β -blockers given the potential to mask symptomatic hypoglycemia. Refer to Section 5.3 for considerations and indications for heart transplantation.

CARDIOLOGY RECOMMENDATIONS

- All patients with GSD IV, including APBD, should receive a comprehensive cardiac evaluation at the time of diagnosis and longitudinal follow-up by a cardiologist.
- The initial evaluation should involve a detailed personal history, family history, and physical exam. Baseline testing which can be considered includes a baseline BNP or NT-proBNP, 12-lead ECG, ambulatory rhythm monitor (such as a Holter monitor), and cardiac MRI with contrast and/or echocardiogram.
- Clinical evaluation including ECG, ambulatory rhythm monitor, and echocardiogram should be repeated annually, or sooner with clinical change. Cardiac MRI with contrast should be repeated at least every 3 to 5 years to monitor for heart disease, or sooner with clinical change.
- Laboratory tests include serum BNP or NT-proBNP periodically (typically every 12 months) to monitor cardiac function and the progression of heart disease, or sooner with clinical change such as new or worsening heart failure.
- A multidisciplinary team including medical genetics, cardiology, cardiac intervention, and cardiac surgery should be consulted when considering whether or not to proceed with mechanical support or cardiac transplantation.
- Monitoring the progression of heart disease and comorbidities of liver/neurological disease is critical to determine the indication for cardiac transplantation and the timing thereof.

5.3. Considerations and indications for liver or heart transplantation

Liver failure occurs in the process of decompensating cirrhosis. Decompensation of cirrhosis is the sign of irreversible liver dysfunction, and liver transplantation is required for long-term survival. To date, liver failure has not been associated with APBD. It is recommended to refer patients to a liver transplantation center before the development of portal hypertension in order to avoid delay in transplantation evaluation. Historically, the diagnosis of hepatic GSD IV prompted liver transplantation in the early stage of life without long-term monitoring of the progression of liver fibrosis, and therefore the natural history of slowly progressive hepatic GSD IV was unclear. Liver disease can progress to end-stage over the course of a few months to 2 to 3 years, yet a significant number of patients have showed mild or even resolution of overt liver disease after years of supportive care [16,23,41,42,71]. Because of the possibility of stability and/or non-progression and lack of available organs, preemptive liver transplantation for patients with GSD IV who do not have decompensated cirrhosis should be avoided. An individualized approach should be taken when considering patients for liver transplantation, even in situations where there is a family history of GSD IV with liver involvement.

Using the same medical criteria for other pediatric liver diseases, patients with hepatic GSD IV should be considered for liver transplantation if they exhibit: (1) evidence of significant liver dysfunction (cholestasis and protein synthesis defects), (2) signs of malnourishment or growth failure despite supplemental enteral feeding with maximal calories, or (3) development of ascites due to portal hypertension, indicating decompensated cirrhosis [121]. For cases with decompensated liver disease, the wait time on the transplantation list will be short as exception Pediatric End-Stage Liver Disease (PELD) scores can be granted for cases with GSD IV in the current United Network for Organ Sharing (UNOS) system. We recommend careful monitoring of liver disease with special attention to ascites and progression of portal hypertension under the care of a pediatric transplantation center, which is also the standard in the management of other hepatic GSDs (types I, III, VI, and IX) [106,107,122]. Considerations for nutrition therapy prior to liver transplantation and post-liver transplantation are detailed in Section 5.11.

Liver transplantation for GSD IV is effective and previous reports demonstrated long-term survival after transplantation [123–126]. The progression of cardiac involvement in GSD IV post-liver transplantation is variable and not well understood. Many cases have successfully received a liver transplant and did not develop cardiomyopathy, yet there are reports of patients who received a liver transplant and subsequently developed severe cardiomyopathy and died from heart failure [43,127,128]. The mechanisms of heart failure after liver transplantation are unclear; however, steroid- and tacrolimus-induced hypertension can cause deterioration of heart function (see Section 5.12). Recent case series of unfavorable outcomes after liver transplantation have highlighted the need for multidisciplinary, longitudinal follow-up of patients post-transplantation to monitor disease progression, as the majority of cases with unfavorable outcomes showed normal heart function on echocardiogram before liver transplantation [43,129]. Therefore, careful evaluation of cardiac function before liver transplantation, even in the absence of clinical decompensation, is warranted. We recommend cardiac MRI in addition to echocardiogram to investigate detailed cardiac function and the presence of myocardial abnormalities as a part of liver transplantation evaluation. The role of heart biopsy and cardiac catheterization needs further investigation. In general, when polyglucosan accumulation is not noted in cardiomyocytes, and cardiac function is intact, the risk of cardiomyopathy after liver transplantation is expected to be low. Yet, when polyglucosan accumulation is found in cardiomyocytes, the degree of accumulation does not predict the risk of heart failure post-liver transplantation [43,124,129].

For cases of GSD IV with cardiomyopathy refractory to medical management, surgical intervention, including mechanical support and

cardiac transplantation, can be considered. It is recommended that decisions to proceed with mechanical support or cardiac transplantation be made in a multidisciplinary fashion seeking expertise from medical genetics, cardiologists specializing in cardiomyopathy and heart failure, cardiac interventionalists, and cardiac surgeons. To date, only two cases of heart transplantation in GSD IV have been reported, both occurring in late adolescence [108,114].

A combination heart-liver transplantation is an option for patients with both heart and liver failure. Although it is technically feasible and has been performed in GSD III patients [131], a combined heart and liver transplantation for patients with GSD IV has not been documented. It is recommended that decisions to proceed with either liver or heart transplantation be made in a multidisciplinary fashion seeking expertise from medical genetics, cardiology, hepatology, and cardiac and hepatic transplantation teams. Further studies of patients with GSD IV and both hepatic and cardiac involvement are needed. At this time, the impact of myopathy and neurologic involvement on liver or heart transplantation outcomes is not clear, and a multidisciplinary approach is needed.

CONSIDERATIONS AND INDICATIONS FOR LIVER OR HEART TRANSPLANTATION

- Liver transplantation is required for long-term survival in individuals with decompensated cirrhosis. Refer to a liver transplantation center before the development of portal hypertension to avoid delay in transplantation evaluation.
 - Liver transplantation should be considered in individuals who exhibit evidence of significant liver dysfunction, signs of malnourishment or growth failure despite supplemental enteral feeding with maximal calories, or development of ascites due to portal hypertension, indicating decompensated cirrhosis.
 - Because of the possibility of stability and/or non-progression and the lack of available organs, preemptive liver transplantation in individuals who do not have decompensated cirrhosis should be avoided.
 - Careful evaluation of cardiac function with cardiac MRI and echocardiogram before liver transplantation, even in the absence of clinical decompensation, should be performed.
 - For cases with cardiomyopathy refractory to medical management, surgical intervention, including mechanical support and cardiac transplantation, can be considered.
 - A combined heart and liver transplantation for patients with GSD IV has not been documented but is an option for patients with both heart and liver failure.
 - The impact of myopathy and neurologic involvement on transplantation outcomes is not clear.
-

5.4. Neurology

5.4.1. Disease expression

Neurologic manifestations of GSD IV can vary in severity and age of onset. Neuromuscular involvement in infancy can manifest as global muscle weakness, hypotonia, arthrogryposis, and respiratory distress, and in children as gross motor delay, hyperlordosis, and proximal weakness. Alternatively, neurologic involvement in APBD typically manifests as spastic gait, neurogenic bladder, and peripheral neuropathy. Natural history studies are needed to understand the progression of neurologic involvement from childhood to late adulthood.

Primarily neurologic manifestations of GSD IV in infancy or early childhood are typically lethal and considered rare, with fewer than 30 cases reported in the literature since Zellweger's initial description of this subtype in 1972 [132]. The reports are almost entirely single case reports [20,53,57,58,60,61,132–136] or reports of multiple individuals in single families [21,52,56,83,84], with only a handful of reports that include multiple unrelated cases [59,100]. All reported childhood cases have had prenatal or congenital onset. Common prenatal signs include fetal akinesia and polyhydramnios. Affected infants are born with congenital hypotonia, often accompanied by contractures (arthrogryposis) and respiratory failure requiring immediate mechanical ventilation. Life expectancy is typically less than one year, due to cardiac and/or respiratory failure. However, there are reported cases of patients who initially resembled the lethal phenotype (global hypotonia and

contractures), but did not require ventilator support or a feeding tube [137]. At latest follow-up, these patients were surviving into middle childhood, but had significant weakness and could not independently ambulate; longitudinal data on these patients is needed.

A neuromuscular-predominant phenotype presenting in late childhood or adolescence has also been reported [16,18,66]. Typically, pregnancy and delivery are normal and there is no cognitive impairment. In two Turkish male siblings, both presented at around 6 to 8 years of age with muscle hypotrophy, weakness, positive Gower sign, and delayed motor development. However, the age of onset and progression is unclear because an additional male sibling was evaluated at age 1.5 years old given the positive family history, and at that time, the patient exhibited muscle hypotonia, mild weakness, and positive Gower sign [16]. In a separate case report, a male patient presented in early childhood with delayed motor development, weakness, and muscle hypotrophy, with progression throughout adolescence [66]. Lastly, another male sibling case report detailed fatigue and generalized skeletal muscle hypotrophy without paresis beginning in early childhood; both siblings suffered from cardiomyopathy, which led to the death in the older sibling at age 19 years [18].

APBD is an adult-onset neurodegenerative disorder where dysfunction of the CNS and PNS is responsible for the most debilitating clinical manifestations: neurogenic bladder (100%), spastic paraparesis (90%), and sensorimotor axonal peripheral neuropathy (90%) [27,138]. The spasticity and neuropathy typically cause motor dysfunction with weakness, impaired rapid and fine movements, muscle cramps, hyper- and/or hypo-reflexia, and joint contractures. In addition, about half of the patients develop late cognitive decline. Initial symptoms and rate of progression are variable, as evidenced by a retrospective study of 50 patients with APBD [27]. Neurogenic bladder was the frequent initial manifestation with a median age of onset of 51 years-old (range 20 to 71 years), and patients reported difficulty walking beginning at a median age of onset of 53 years (range 33 to 65 years), with progression to a wheelchair-bound state at a median age of 64 years (range 51 to 73 years). Sexual dysfunction, including male impotence, was often reported but not systematically assessed, so prevalence is uncertain. Additional neurologic manifestations in less than half of the patients include abnormal eye movements with saccadic pursuit and occasional loss of convergence, arm spasticity, cerebellar ataxia, dysautonomia with orthostatic hypotension, fecal incontinence, and parkinsonism with bradykinesia [138]. Cognitive decline consisting of mild to moderate attention and memory deficit may also affect up to 50% of patients with APBD [27], and a recent review of published cases found that executive deficits and memory impairment are the most common cognitive symptoms in APBD [139].

A diverse range of neurons and neural tracts can be affected in APBD, leading to symptomatic overlap with disorders across the neuromuscular and CNS spectrum, including: stroke-like events with leukodystrophy [140], pure or complicated hereditary spastic paraplegia [141], ALS-like motor neuron disease [95,142], atypical parkinsonism with upper motor neuron disease [92,143,144], frontotemporal dementia with motor neuron disease [145–148], asymmetric progressive plexopathy predominantly affecting the brachial plexus [149], relapsing-remitting neurological manifestations with hepatopathy [33], leg myoclonus, bulbar palsy, and ophthalmoplegia [144,151], and severe diaphragmatic dysfunction with respiratory failure [91].

5.4.2. Evaluation and management

Comprehensive physical examinations in infants, children, adolescents, and adults should be performed with special attention to neuromuscular function, including assessment of muscle tone, bulk, and strength.

For pediatric patients, growth and developmental milestone acquisition should be monitored. In individuals with contractures where accurate height/length measurements cannot otherwise be obtained, alternative measurement methods are detailed in Section 5.13. Due to

the spectrum of neurologic involvement in GSD IV, the progression of classical childhood/adolescent neuromuscular symptoms into symptoms consistent with APBD is a possibility, and lifelong monitoring is warranted. Moreover, pediatric patients with GSD IV and predominantly hepatic involvement initially have gone on to exhibit neuromuscular involvement [29] and therefore longitudinal evaluations by a neurologist are warranted in all pediatric patients with GSD IV to monitor disease progression. In all symptomatic pediatric patients with neuromuscular involvement, regardless of age of onset, serum CK levels may be normal [16,52,66,132,135,136] or mildly to moderately elevated [20,53,56–58,61,133]. When performed, nerve conduction studies (NCS) and electromyography (EMG) tend to demonstrate myopathic features [16,18,20,57,58,61,100,132,133,135], with some hints of neurogenic findings in scattered cases [60,100]. Both EMG/NCS and skeletal muscle imaging can be supportive of the diagnosis, but have a limited role in dictating symptomatic management of pediatric patients with GSD IV; they can be considered if disease progression follows unexpected patterns or if unexpected neurologic complications arise.

In APBD, because nervous system involvement is extensive, brain and spinal cord (cervical and thoracic) MRIs can assist in disease diagnosis by revealing white matter lesions and atrophy. MRI abnormalities can have a posterior predominance and diffuse cerebral, cerebellar, or frontotemporal cortical atrophy, and are typically accompanied by diffuse leukoencephalopathy with lesions in the subcortical and periventricular white matter, pontine medial lemniscus, dentate nucleus, posterior limb of the internal capsule, external capsule, anterior medulla oblongata, and cerebellar peduncles [27]. Spinal cord atrophy typically develops without discrete lesions. White matter lesions may resemble those observed in MS or vascular leukoencephalopathies [27]; however, unlike MS, the lesions do not enhance with contrast. Brain, spinal cord, and skeletal muscle MRIs support diagnosis and understanding of the individual's disease progression but have limited roles in dictating symptomatic management; routine brain and spinal cord MRIs without contrast are recommended every 2 to 5 years to document longitudinal progression. Neuroimaging can be repeated earlier if disease progression follows unexpected patterns or when unexpected neurological complications arise.

APBD is considered both an upper and lower motor neuron disease, and NCS and EMG typically demonstrate signs of axonal sensorimotor polyneuropathy or lumbosacral polyradiculopathy with chronic denervation abnormalities and mild acute denervation changes. Autonomic testing often reveals abnormalities in cutaneous sympathetic reflex responses and thermoregulatory sweat testing, as well as reduced or absent cutaneous vasoconstriction reflexes [27,138]. Repeat electrodiagnostic procedures have a limited role in dictating symptomatic management, but should be considered when disease progression follows unexpected patterns or when unexpected neurological complications arise.

Treatment of neurologic manifestations in GSD IV, including APBD, are primarily symptomatic and best managed by multidisciplinary teams with specialists dictated by the disease manifestations. There are no disease-modifying therapies currently available and there are no biomarkers that have been validated for predicting or monitoring neurologic progression. The care of infants with the severe neuromuscular form of GSD IV has been supportive to date, primarily focusing on mechanical ventilation and other critical care interventions. In addition to being followed by a neurologist, individuals affected by the childhood, adolescent, or adult form of the disease, including APBD, should be followed by a physical therapist and/or occupational therapist (see Section 5.6) to monitor for changes in motor function, prevent and delay progression of impairments, preserve muscle function and mobility, optimize physical function, maintain independence, and for prescription of durable medical equipment (i.e., orthotics). All patients with APBD should be routinely screened for bulbar involvement (i.e., dysfunction of speech and swallowing) given the risk of silent aspiration and subsequent infection, and should be referred for further

assessment and treatment by appropriate rehabilitation specialists, such as a speech-language pathologist, as needed.

Additionally, for APBD, patients typically require urological interventions under the care of a urologist and referral to pelvic floor rehabilitation (see Sections 5.5 and 5.6). Anti-spasmodic drugs may alleviate skeletal muscle spasms and cramps. As the disease progresses and gait impairment worsens, patient requirements for assistive devices may increase from support with a cane, to walkers, and ultimately to wheelchairs. Manifestations of dysautonomia, such as orthostatic hypotension, should be managed symptomatically. Complaints of rapid vision loss, haziness in vision, and changes in contrast sensitivity have been noted in the APBD population [7,152–155]; if vision suddenly changes, a referral to an ophthalmologist with expertise in neurological conditions is recommended. The disease pathology within the gastrointestinal tract is not well understood. Reports of irritable bowel disease, fecal incontinence, constipation, and poor rectal sphincter tone have been noted in the APBD population [77,85,190,191] and require referral to a gastroenterologist.

NEUROLOGY RECOMMENDATIONS

- All patients with GSD IV, including APBD, should receive neurologic evaluation at the time of diagnosis and then periodically thereafter.
- Treatment of neurologic manifestations are primarily symptomatic.

Additional recommendations for pediatric-onset GSD IV:

- The care of infants with the severe neuromuscular form of GSD IV is currently supportive.
- Regardless of age of onset, referral to physical and/or occupational therapy is warranted to monitor for changes in motor function, prevent and delay progression of impairments, and optimize functional outcomes.
- Clinical evaluations including an EMG/NCS and skeletal muscle imaging may be useful during the diagnostic process, but have limited roles in guiding longitudinal management. They may be helpful when the disease course follows unexpected patterns or when unexpected neurologic complications arise.

Additional recommendations for APBD:

- Clinical evaluations including an EMG/NCS and MRI of the brain and/or spinal cord support diagnosis. Initial brain MRI with contrast can be useful to distinguish APBD from multiple sclerosis.
- Repeat EMG/NCS have limited roles in guiding longitudinal management and should be considered when the disease course follows unexpected patterns or when unexpected neurologic complications arise.
- Routine brain and spinal cord MRIs without contrast are recommended every 2 to 5 years to document disease progression.
- Neurogenic bladder manifestations require management by a urologist.
- Referral to physical and/or occupational therapy is warranted to monitor for changes in motor function, prevent and delay progression of impairments, and optimize functional outcomes.
- Manifestations of dysautonomia, such as orthostatic hypotension, should be managed symptomatically.
- Referral to an ophthalmologist is recommended if vision suddenly changes.

5.5. Urology

5.5.1. Disease expression

Bladder dysfunction is not well documented in pediatric patients with GSD IV, with limited reports indicating that patients could suffer from nocturnal enuresis [156]. The urologic manifestations of APBD includes neurogenic lower urinary tract dysfunction (i.e., neurogenic bladder) with symptoms ranging from frequent, urgent urination with or without urinary incontinence to hesitancy, slow urinary stream, difficulty emptying, or even complete urinary retention. Recurrent urinary tract infections (UTI), while multifactorial, can be a manifestation of poor bladder emptying. Although less well studied, erectile dysfunction is also a common complaint among men with APBD [27]. Urinary symptoms are a hallmark of APBD, often occurring as the first symptom, sometimes one to two decades before the onset of gait disturbance or sensory deficits. It is hypothesized that the onset of bladder dysfunction may correlate with the degree of medullary and spinal atrophy [157].

Progressive neurogenic bladder has been reported as early as 35 years of age [140]. In a 2012 analysis of 50 patients with APBD, 100% had “neurogenic bladder” at a median age of onset of 51 years [27]; however, it is unclear what the distribution of bladder symptoms was and whether they were primarily overactive symptoms (e.g., frequency, urgency, nocturia, incontinence) or obstructive/emptying symptoms (e.g., hesitancy, straining to urinate, slow stream, urinary retention) or both. The constellation of urinary symptoms is important as there are recognized patterns of neurogenic bladder, with the location of neurologic insult (whether it be in the brain, brainstem, level of spinal cord, or peripheral nerves) influencing the type of bladder dysfunction produced and the potential risk of UTI and renal compromise imposed on the patient.

Additional work is needed to understand the mechanisms involved in bladder dysfunction in APBD, but current knowledge suggests it can result from disruption of either the CNS or PNS innervation of the bladder. The pons, specifically the pontine micturition center, is an important part of the central circuitry that regulates bladder function and lesions above and below the pons classically produce different mechanisms of bladder dysfunction (with some exception). Like MS, APBD can affect the brain above and below the pons. We can anticipate that as we learn more about the bladder complaints in men and women with APBD, the bladder experiences may vary widely. Additional studies will be needed to determine if polyglucosan bodies accumulate in the bladder, urethral sphincter, pelvic and/or peripheral nerves, and to elucidate the mechanisms that impact bladder function.

5.5.2. Evaluation and management

For all patients with GSD IV, particularly APBD, screening for urinary tract involvement is highly recommended. Simply asking the patient, “Has anything changed with your bladder?” is likely to identify those in need of evaluation. At this time, there are no specific patient-reported outcome questionnaires for neurogenic bladder, general bladder dysfunction/incontinence, or erectile/ejaculatory dysfunction that have been validated for use in the APBD population. For those who have lower urinary tract symptoms, urologic evaluation should be performed by a urologist, preferably one trained in neurogenic lower urinary tract dysfunction (i.e., neuro-urologist). Evaluation should include a careful symptom history, physical exam, urinalysis, and measurement of a post-void residual urine volume if the patient is able to void spontaneously [158]. If the patient is deemed low-risk, no additional testing is required. For unknown or elevated risk patients, renal imaging, renal function assessment, and urodynamic testing should be obtained. Importantly, impaired bladder compliance (loss of viscoelastic properties of the bladder) as a cause of hydronephrosis or renal compromise should be identified promptly to prevent renal compromise. Follow-up and ongoing surveillance are important since symptoms and underlying dysfunction can change over time. For moderate risk patients, annual evaluation with bladder symptom assessment, renal functional assessment and biennial upper tract imaging should be performed [158]. In high-risk patients, annual renal imaging and urodynamics are recommended. In asymptomatic patients, surveillance urine testing should not be performed and asymptomatic bacteriuria should not be treated. Patients with recurrent urinary tract infections, hematuria, or concern over anatomical abnormality should undergo upper tract imaging and cystoscopy [158]. Repeat hospitalizations for urinary tract infections and related complications are common in APBD; therefore, patients and their care providers should be educated on the early signs and symptoms of infections.

Existing consensus guidelines on neurogenic lower urinary tract dysfunction [158] and overactive bladder [159] can inform the approach to treatment of bladder symptoms in patients with APBD, allowing for an individualized approach based on a preponderance of overactive versus obstructive/emptying urinary symptoms. For patients with urgency, frequency, nocturia, and incontinence first-line treatment includes behavioral modifications such as fluid modulation (or restriction prior to

going to bed), elimination of bladder irritants (e.g., caffeine, alcohol), timed voiding (i.e., voiding before urgency or incontinence typically occurs) and optimizing bowel function as well as pelvic floor muscle exercises. Second-line treatment includes bladder control medications (e.g., antimuscarinics, β 3-agonists); third-line treatment includes botulinum toxin injection into the bladder and neuromodulation of the sacral or tibial nerves. Desmopressin can be used with caution to manage nocturia. For patients with hesitancy, straining, slow stream, or emptying difficulties, first-line treatments include timed voiding, double voiding (i.e., attempting to void again immediately after going), optimizing bowel function, and pelvic floor muscle exercises geared toward improving relaxation and tone (see [Section 5.6](#)). Titrating muscle relaxants can be helpful in promoting pelvic floor relaxation during voiding. α -blockers can be trialed to improved urinary flow and emptying, but there is limited data on efficacy, especially in women. When emptying is not adequate, clean intermittent self-catheterization is recommended over placement of an indwelling catheter to decrease the risk of recurring UTI. If clean intermittent self-catheterization is not possible, one can consider a suprapubic catheter for ease of catheter exchanges; a suprapubic tube is preferred over a urethral catheter to minimize risk of urethral erosion. There is no difference in risk for UTI between suprapubic catheters and urethral catheters [160]. Occasionally, reconstructive procedures to augment the bladder and build a catheterizable channel may be needed. It is expected that patients with APBD may in fact have a combination of overactive and obstructive/emptying bladder symptoms and may need combination therapy (e.g., intermittent catheterization plus botulinum toxin injection) to diminish urinary symptoms.

UROLOGY RECOMMENDATIONS

- All patients with GSD IV, particularly in APBD, should be screened for urinary tract involvement at the time of diagnosis and during longitudinal follow-up.
- Ongoing surveillance for urinary tract involvement is important since symptoms and underlying dysfunction can change over time.
- In asymptomatic patients, surveillance urine testing is not necessary and asymptomatic bacteriuria should not be treated.
- Patients with recurrent urinary tract infections, hematuria, or concern for anatomical abnormalities should undergo imaging and cystoscopy.
- Existing consensus guidelines on neurogenic lower urinary tract dysfunction can inform treatment and management approaches, including the use of behavioral modification, medications, botulinum toxin injection, neuromodulation, and catheterization.
- Additional work is needed to understand the mechanisms involved in bladder dysfunction in APBD.

5.6. Rehabilitation therapy

Given the wide range of neurological and neuromusculoskeletal involvement associated with reduced or deficient GBE activity, and the heterogeneity in terms of tissue involvement, age of onset, and clinical manifestations, all patients require comprehensive, individualized assessment to monitor disease presentation and progression and identify opportunities for intervention. The underlying neurological pathologies are reflected by a range of clinical manifestations, with symptoms occurring across a range of ages and severity with overlap between diagnostic categories. Clinical surveillance should include scrutiny in assessment regarding these features in all individuals throughout the lifespan. This section focuses on the role of physical and occupational therapy which is essential to monitor for changes in motor function, prevent and delay progression of impairments, preserve muscle function and mobility, optimize physical function, and maintain independence. In addition to physical and occupational therapy, all patients with bladder and/or bowel dysfunction should be referred to pelvic floor rehabilitation, also known as pelvic floor muscle training, for expertise in pelvic muscle strengthening, endurance, power, relaxation, and coordination exercises. Patients with changes or difficulty in speech

and/or swallowing, suggesting bulbar involvement, should be referred for further assessment and management by a speech-language pathologist. Additional rehabilitation specialties should be considered based on the individual patient's needs and symptoms.

Individuals with GSD IV, including APBD, may present with a range of symptoms and functional limitations that reflect the effects of their individual underlying myopathic and neurologic involvement. Some patients with GSD IV present with predominantly neuromuscular manifestations during infancy or early childhood, including hypotonia, weakness, and/or muscle atrophy, contractures respiratory distress, failure to thrive, fatigue, pain, and delay in the achievement of motor skills. Importantly, however, even patients who present with predominantly hepatic manifestations require careful evaluation for concurrent motor impairments, as these patients have also been reported to exhibit gross motor delay, hypotonia, and other neuromuscular manifestations [29]. Cardiac involvement also has the potential to contribute to decreased exercise tolerance. For adults with APBD, a range of additional disease manifestations may contribute to functional limitations, including neurologic-based impairments in motor control and function, peripheral neuropathy, spasticity, weakness, dysautonomia, and neurogenic bladder.

Motor manifestations may be based on myopathic and/or neurologic (CNS and/or PNS) involvement, as detailed in [Section 5.4](#). Clinical features in the motor system can therefore include (1) primary muscle weakness from myopathy (including skeletal muscle weakness and cardiomyopathy), (2) neurologic-based hypotonia and other abnormalities of muscle tone including spasticity, (3) sensory losses, (4) autonomic dysreflexia, (5) impairment of motor control, balance, and coordination, (6) urinary incontinence, and (7) cardiorespiratory compromise. Functional ramifications may include difficulty overcoming gravity, difficulty in activities of elevation against gravity as in other neuromuscular disorders with the use of Gower's maneuver and other classic compensatory movements during transitions between positions, and effects on posture during movement including gait such as lumbar lordosis, fatigue, decreased endurance, delay in the attainment of motor skills, failure to thrive, diaphragmatic failure, and impaired function in mobility and gait.

In addition to the primary effects of polyglucosan accumulation, individuals with GSD IV, including APBD, may develop secondary worsening of neuromuscular function due to disuse and deconditioning, and/or the development of secondary musculoskeletal impairments such as contracture and deformity. Secondary musculoskeletal involvement may occur early from fetal akinesia with contractures presenting at birth (arthrogryposis) or may evolve slowly over time secondary to chronically decreased or compromised patterns of movement and chronic abnormal postures as in other neuromuscular disorders (i.e., Duchenne muscular dystrophy, spinal muscular atrophy). Compromised movement may also lead to the risk of compromised skin integrity with repeated hospitalizations for pressure wounds (also referred to as bedsores) and related complications, and therefore, patients and their care providers should be educated on preventative care and the early signs and symptoms of infections.

Physical and occupational therapy examination, evaluation, and intervention are important across all domains of the World Health Organization's International Classification of Function, Disability, and Health (ICF), especially for those individuals with neurological, musculoskeletal, and cardiorespiratory involvement. The choice of assessment and intervention should be individualized based on age, system involvement, and presentation of features. Physical and occupational therapy assessments should include measures of muscle tone including hypotonia and spasticity, motor control and coordination, balance, postural control, and function, measures of strength, passive joint ranges of motion and muscle extensibility, posture and alignment of the spine and extremities, identification of hypermobility as well as contracture and deformity, reflex activity, sensation, pain, identification of the risk of secondary musculoskeletal impairments, risks and early signs and

symptoms of compromised skin integrity, cardiorespiratory status and function, and bowel and bladder function. In addition to standard impairment level measurements, functional assessments, measures of disability, fatigue scales, and patient-reported outcomes are important and valuable tools for evaluation at baseline and over time (Supplementary Table S1). The choice of measures to be used should be tailored to the individual's age, clinical presentation, comorbidities, functional status, and personal goals, and should include all categories of the ICF. For all individuals with GSD IV, including APBD, longitudinal physical and occupational therapy follow-up is indicated to monitor for changes in neurological and musculoskeletal function over time, prevent or delay the progression of secondary impairments, and offer interventions aimed at optimizing function and participation, including assistive technology as needed.

Physical and occupational therapy can assist the multidisciplinary team by providing comprehensive, anticipatory, preventative management including optimizing strength and motor control, facilitating motor development, maintaining or improving joint range of motion and muscle extensibility and preventing/decreasing contracture and deformity, managing spasticity and the impact of spasticity, preventing/decreasing pain, protecting and optimizing skin integrity, optimizing cardiorespiratory status and function, optimizing bowel and bladder function and management, improving function including ambulation, and recommendation of adaptive equipment and assistive technology for musculoskeletal management and to optimize function and functional independence. Minimizing secondary worsening of neuromuscular function due to disuse and deconditioning is also important and should focus on maximizing function and minimizing secondary deterioration. Musculoskeletal management should utilize principles of developmental biomechanics to minimize secondary musculoskeletal impairment, including contracture and deformity, with prolonged passive stretch, which may be facilitated by splinting and orthotic intervention, serial casting, and positioning devices. Strengthening and exercise recommendations in the presence of myopathic involvement should follow standard guidelines for the protection of fragile muscles in the presence of myopathy, including the use of submaximal functional exercise, avoidance of excessive resistive and eccentric exercise, individual monitoring of rate of perceived exertion, cardiorespiratory monitoring, optimizing biomechanics, and energy conservation. Therapeutic exercise recommendations in the presence of neurologic manifestations such as decreased coordination, spasticity, and lack of isolated control should include neurodevelopmental therapeutic handling techniques that inhibit abnormal muscle tone and facilitate selected control of degrees of freedom in more normal patterns of movement, followed by practice of functional movement and tasks. Adaptive equipment, assistive technology, and orthotic devices should be used as needed to support movement and musculoskeletal management, maintenance of skin integrity, safety, energy conservation, and participation.

PHYSICAL REHABILITATION RECOMMENDATIONS

- All individuals with GSD IV, including APBD, should be followed by physical rehabilitation specialists to monitor and optimize neuromusculoskeletal status and function over time, prevent or delay the progression of secondary impairments, and offer interventions aimed at optimizing function and participation, including assistive technology as needed.
- Areas for assessment include direct assessment and the use of patient-reported outcomes in the following areas: neurological, musculoskeletal, cardiorespiratory, integumentary, bowel and bladder, function, fatigue, pain, disability, quality of life, and adaptive equipment & assistive technology.
- Areas for intervention and monitoring, even in individuals in whom symptoms have not yet been reported, include exercise (strengthening and/or optimizing movement, protection of fragile muscles), managing abnormal muscle tone, optimizing motor control and functional coordinated movement (including gait), energy conservation, cardiopulmonary care, bowel and bladder management, maximizing function, minimizing deconditioning, fatigue, and pain, as well as prevention, minimization, and management of secondary contracture and deformity, and offering recommendations regarding adaptive equipment and assistive technology.

- Patients and their care providers should be educated on preventative care and the early signs and symptoms of infections due to risk of compromised skin integrity with repeated hospitalizations for pressure wounds (also referred to as bedsores).
- All patients with bladder and/or bowel dysfunction should be referred to pelvic floor rehabilitation for expertise in pelvic muscle strengthening, endurance, power, relaxation, and coordination exercises.
- The role of additional rehabilitation specialties, including speech-language pathology, should be considered based on the individual patient's needs and symptoms.

5.7. Fatigue and physical activity

The mechanism of fatigue in both children and adults with GSD IV is not well understood and is likely multifactorial. Contributing factors could be due to disease pathology, impairment of neuronal function, lack of muscle strength, poor sleep due to end-stage liver disease status, neurogenic bladder, pain, or abnormal sleep as shown in other white matter and mood disorders (see Section 5.8). Polysomnography (sleep study) should be conducted to assess for sleep apnea. Routine physical activity, specifically mild to moderate aerobic exercise, should be encouraged in all individuals. Stretching and warming up should be performed prior to activity. Exercises targeted to flexibility and strengthening of the core muscles are particularly important in individuals demonstrating or at risk of decreased range of motion and hypotonia, respectively. Patients should be encouraged to avoid potentially damaging activities, including heavy weightlifting and intense resistive and eccentric activity. Individuals with severe cardiac dysfunction should receive clearance from a cardiologist before implementing an exercise regimen. Individuals with hepatosplenomegaly and/or signs of liver dysfunction should avoid contact sports, as these place the patient at increased risk for hepatic/splenic injury and bleeding. Physical and/or occupational therapy services may be utilized to preserve muscle function, mobility, maintain independence, develop a safe exercise regimen, and use energy conservation techniques to support function and optimize participation (see Section 5.6). Medications that target nerve signals have been shown to improve walking speed in other demyelinating disorders (i.e., MS) and can be considered for APBD.

5.8. Psychology

The extent to which the GSD IV disease pathology impacts cognition is unclear. Neuropsychological evaluations are recommended to define the individual's level and type of impairment, if any, and can be treated with patient-tailored cognitive behavioral therapy and psychopharmacology, as appropriate.

To date, cognitive decline has only been attributed to APBD and there is no standard treatment for the cognitive decline and psychiatric manifestations seen in APBD. The lack of awareness of this disorder within the healthcare system leads to feelings of isolation and desperation for answers in the patients. Despite the different pathophysiology of neurodegenerative diseases, psychiatric symptoms have been seen across all neurodegenerative disorders [161]. While there has been no formal research on the psychiatric symptoms seen in APBD, it is assumed that the disease would fall within the spectrum of other neurodegenerative disorders, and it is likely that both the pathophysiology of the disease and the emotional trauma of the diagnosis cause the psychiatric symptoms [162]. Moreover, the psychiatric symptoms of a neurodegenerative disease can be more difficult to distinguish in the advanced stages due to overlap with functional and cognitive decline [161]. Different neurologic conditions share common psychiatric features, such as anxiety, depression, and apathy. Anxiety can present as irritability, paranoia, and emotional instability [161], and a diagnosis of depression can be difficult to distinguish from the overlapping neurologic symptoms such as fatigue, insomnia, and cognitive dysfunction [163]. Loss of independence and uncertainty about the future can add to the despair. However, the psychopathological manifestations can show distinct patterns of symptoms depending on the disease and the

individual. Acknowledgement and management of psychiatric symptoms such as anxiety and depression can improve emotional adaptation and quality of life for the patient, and the use of anti-anxiety and/or antidepressant medications should be individualized. The course of psychiatric disease features can vary as well (remain stable, progress, or decrease in severity) [161], and the progressive and fatal nature of a neurodegenerative disorder can impact the psycho-emotional experiences of the patient [164]. Living with a neurological disease has a profound effect on almost all facets of life, including self-image, family, and social relationships. Research on the psychological symptoms and unique psychosocial impacts in APBD is warranted to encourage accurate diagnosis and adequate treatment.

5.9. Care, coordination, and support

As a part of the multidisciplinary care team, a metabolic specialist or other team member experienced with GSD IV should coordinate the patient's care to ensure the best health outcomes and facilitate regular communication about the health of the patient. This team member can also facilitate a referral to a social worker who can coordinate healthcare recommendations, including family planning and psychosocial considerations. It is also important for the affected individuals and their support systems to be connected to community organizations that can provide mental and emotional support. Several patient advocacy and research organizations are available for individuals and families with GSD IV, including APBD. The AGSD (<http://www.agsdus.org>) provides information and support to individuals and families affected by GSD. The website provides descriptions of the GSD types and provides opportunities for the GSD community to connect, including an annual conference and virtual community groups. The APBD Research Foundation (<http://www.apbdrf.org>) is dedicated to finding a cure for APBD while improving the lives of individuals and families affected. They also increase public awareness and understanding of the disease, especially in the at-risk Ashkenazi Jewish population and across the medical community. Both the AGSD and the APBD Research Foundation support research studies that may lead to new treatment options and a cure for the many phenotypes of GSD IV.

5.10. Genetic counseling, prenatal diagnosis, and screening

Genetic counseling should be offered to all families of children and adults with GSD IV, including APBD. Genetic counselors can help families understand risk to current or future family members, discuss family planning and prenatal diagnosis, and provide information about research and new therapies.

GSD IV, including APBD, is inherited in an autosomal recessive manner. When counseling these individuals/families, the genetic counselor should collect at least a three-generation pedigree from the proband/family. De novo variant rates in *GBE1* are expected to be infrequent; parents of an affected individual are assumed to be obligate heterozygotes (i.e., carriers of one *GBE1* pathogenic variant). Each sibling of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Each sibling of the proband's parents is at 50% risk of being a carrier of a *GBE1* pathogenic variant. Carrier testing using molecular assays is available if the familial pathogenic variants are known. GBE activity analysis is not recommended for carrier testing. Variant analysis to further refine the risk of having a child with GSD IV can be offered to those at risk (e.g., the spouse of a known carrier or spouse of an affected person). *GBE1* is often included in prenatal screening panels for individuals of Ashkenazi Jewish background [8]. Prenatal diagnosis is clinically available and if the family's variants are not known, *GBE1* sequencing can be performed on cultured chorionic villus samples or amniocytes; alternatively, or if the family's variants are not known, enzyme analysis can be performed on cultured chorionic villus samples or amniocytes and these results need to be confirmed through molecular testing.

Preimplantation genetic diagnosis is available once the *GBE1* pathogenic variants have been identified in an affected family member.

Inclusion of *GBE1* in diagnostic gene testing for pediatric-onset hepatopathies, cardiomyopathies, and neuropathies, as well as adult-onset neuropathies is warranted. Given that APBD is often misdiagnosed as a different neurodegenerative disorder, such as MS, ALS, hereditary spastic paraplegia, or Parkinson's disease, *GBE1* should be included on diagnostic adult neuromuscular, neurodegenerative, and leukodystrophy gene panels.

GENETIC COUNSELING/PRENATAL DIAGNOSIS/SCREENING RECOMMENDATIONS

- Genetic counseling should be offered to all parents with a child with GSD IV and to all adults with GSD IV, including APBD.
 - Determine the proband's *GBE1* variants when feasible for diagnosis and to direct further testing for family members.
 - *GBE1* variant information is important for carrier testing or prenatal diagnosis and can be used for targeted variant analysis if clear knowledge of specific private family variants and/or common variants for specific ethnic groups is available.
 - When both variants are known, molecular testing is the preferred method for prenatal diagnosis.
 - It is recommended to include *GBE1* in diagnostic gene panels for pediatric-onset hepatopathies, cardiomyopathies, and neuropathies, as well as panels for adult-onset neuromuscular, neurodegenerative, and leukodystrophy disorders.
-

5.11. Nutrition considerations and energy availability

Despite GSD IV being a result of accumulation of abnormally structured glycogen (both a quantitative and qualitative defect), the role of altered glycogen synthesis on glycemic control and subsequent risk of cellular energy deficits and hypoglycemia is not well understood. It is thought that GBE deficiency does not cause hypoglycemia even in infants who have less fat and glycogen storage than adults [97]. Rather, it has been suggested that hypoglycemia in GSD IV occurs in the context of impaired hepatocyte function and reduced gluconeogenesis secondary to liver failure. Yet, the mechanisms contributing to energy deficits and/or hypoglycemia remain unclear. It is thought that the continued activation of GYS potentially contributes to an overall energy deficit in the cell because it continually limits adenosine triphosphate (ATP) availability which then activates AMP-activated protein kinase (AMPK) and subsequently inactivates serine/threonine residues of intermediate anabolic enzymes via phosphorylation [165]. Chronic activation of AMPK is not beneficial in the setting of a catabolic defect (i.e., the inability to degrade polyglucosan in GSD IV); thus, reversal of this continuous AMPK activation requires anaplerotic therapy [165]. Accordingly, triheptanoin (an odd chain fatty acid) diet therapy was suggested for its anaplerotic effects to treat the energy defect in APBD [165,166]. Results of a randomized, double-blinded, placebo-controlled study using triheptanoin (C7:0) for 6 months in patients with APBD showed that triheptanoin was safe, but the study could not determine if it was effective in this patient population [28].

At this time, there is no published evidence on the use of dietary intervention in patients with GSD IV with primarily neuromuscular, neurologic, or cardiac involvement (with the exception of the triheptanoin trials [28,166,167]). Rather, emphasis on the use of dietary management has been noted only in those with hepatic involvement and recommendations depend upon the progressive nature of the disease. Hepatic disease progressing to liver failure results in impairment of carbohydrate, protein, and fat metabolism, resulting in protein-energy malnutrition, growth failure and nutrient deficiencies, particularly deficiency of fat-soluble vitamins. Hence, dietary treatment should aim at ensuring adequacy of all the macronutrients and micronutrients. Fat-soluble vitamin supplements are indicated in cases with cholestasis. The hepatologist and metabolic dietitian should take the extent of liver failure into account when recommending nutrition therapy in patients with hepatic GSD IV. Cirrhosis leads to a state of hypermetabolism and increased

energy needs in children. Protein restriction is not recommended with cirrhosis unless clinically significant hyperammonemia persists. The development of ascites and portal hypertension necessitates sodium and fluid restriction. Parenteral nutrition is frequently used to improve growth and nutritional status prior to liver transplantation, despite maximum enteral therapy in children. A cautious approach against aggressive use of parenteral nutrition is recommended due to major risk of associated hepatic disease. Steatosis due to excessive glucose, azotemia due to excessive protein, and hypertriglyceridemia and progression of hepatic disease due to excessive lipids in the parenteral nutrition solution are known complications. Enteral starvation is a critical factor in the pathogenesis of total parenteral nutrition-related hepatic disease and hence early initiation of enteral feedings is highly recommended. There is limited evidence to show clinical benefit of using parenteral nutrition formulations high in branched-chain amino acids in hepatic disease. Use of a high-protein diet as a source of gluconeogenesis, a bedtime snack, and tube feedings are other recommendations for hepatic GSD IV to optimize growth and nutritional status prior to liver transplantation. We recommend careful monitoring of glucose levels in patients with severe liver dysfunction during an acute decompensation.

Despite the mechanisms of hypoglycemia in GSD IV remaining unclear, the use of nutrition therapy in hepatic GSD IV has been described. Goldberg and colleagues described one 18-month-old male with hepatic GSD IV who, prior to receiving a liver transplant, received a diet high in protein and low in carbohydrates; he showed improved growth and weight with stable liver function [168]. Fasting-induced hypoglycemia has been reported with the progression of cirrhosis in hepatic GSD IV. Two patients with hepatic GSD IV and asymptomatic fasting hypoglycemia by age 13 months were treated with frequent feedings, addition of uncooked cornstarch (UCCS), and overnight feedings with the goal of maintaining normoglycemia and adequate nutrient intake [81]. This nutrition management was shown to improve fasting tolerance, growth, muscle strength, and improve liver function [81]. After several months of dietary therapy, one of these patients began refusing feedings then deteriorated, ultimately dying from esophageal hemorrhage at age 22 months. In the remaining patient, liver function was maintained until liver transplantation was successfully performed at age 17 months. An additional case report of a patient with hepatic GSD IV described improvement of liver size, growth, and liver function with a high-protein and carbohydrate-restricted diet; the patient was 17 years old at the last follow-up, with a normal sized liver and no evidence of liver function abnormalities [78]. A retrospective, observational, longitudinal case series of 15 patients with GSD IV reported efficacy of high-protein diets, use of UCCS, late night meals, and overnight tube feeding in improving clinical and biochemical outcomes and delaying or preventing liver transplantation [40]. However, detailed and objective data on hypoglycemia and ketone levels in the context of hepatic and neuromuscular involvement severity is needed to support these conclusions and establish universal dietary recommendations for all patients with hepatic GSD IV. Whether a supplemental cornstarch diet can be associated with favorable outcomes remains an open discussion [40].

All patients, regardless of age, should be followed by a metabolic dietitian who can provide individualized dietary recommendations. Dietary treatment should be individualized based on the specific patient's condition and stability and should aim to avoid catabolism and prevent polyglucosan formation. Considerations for dietary treatment include growth parameters, liver disease severity, extent of dysphagia and ability to swallow, urinary incontinence, gastrointestinal symptoms, and severity of pressure wounds. If the patient has dysphagia, food texture, consistency, and fluid intake need to be adjusted appropriately and a speech-language pathologist should be consulted for management. The main consideration for nutrition care is maintenance of healthy body weight while maintaining a nutrient-rich diet with inclusion of complex carbohydrates (low glycemic index) and limitation of simple carbohydrates (high monosaccharide content). In all patients with

GSD IV, including APBD, limiting total and simple carbohydrates is considered to be beneficial to prevent accumulation of abnormally formed glycogen (polyglucosan). Glucose levels should be monitored on an individual basis. For patients with a history of hypoglycemia and/or hyperglycemia, continuous glucose monitoring systems are useful in the management of metabolic control. The safety and efficacy of a ketogenic diet or intermittent fasting in GSD IV have not been described. There is no data on the impact of breastfeeding or infant formula on GSD IV progression; unless otherwise contraindicated, infants should be breastfed or provided standard infant formula according to the American Academy of Pediatrics [169] and WHO policy recommendations to support growth and development. Considerations for the nutrient composition of foods for infants transitioning to solid foods should be directed by a metabolic dietitian. Additional research into the prevalence and mechanisms of hypoglycemia, as well as the use of dietary treatment in GSD IV, is critically needed.

NUTRITION RECOMMENDATIONS

- All patients with GSD IV, including APBD, should receive individualized dietary recommendations based on the individual patient's condition and stability as directed by a metabolic dietitian.
- Dietary treatment should ensure maintenance of healthy body weight while providing a nutrient-rich diet with inclusion of complex carbohydrates (low glycemic index) and limitation of simple carbohydrates (high monosaccharide content). Limiting total and simple carbohydrates is considered to be beneficial to prevent accumulation of polyglucosan.
- Considerations for dietary treatment include growth parameters, liver disease severity, extent of dysphagia and ability to swallow, urinary incontinence, gastrointestinal symptoms, and severity of pressure wounds.
- The mechanisms contributing to energy deficits and/or hypoglycemia in GSD IV, including APBD, remain unclear.

Additional recommendations for patients with liver disease:

- Protein restriction is not recommended with cirrhosis unless clinically significant hyperammonemia persists.
- Supplementation of fat-soluble vitamins is indicated in cases with cholestasis.
- Development of ascites and portal hypertension necessitates sodium and fluid restriction.
- Parenteral nutrition is frequently used to improve growth and nutritional status prior to liver transplantation, but an aggressive approach should be used with caution due to major risk of parenteral nutrition-related hepatic disease.
- Use of high-protein diet as a source of gluconeogenesis, a bedtime snack, and tube feedings are recommended to optimize growth and nutritional status prior to liver transplantation.
- Glucose levels should be carefully monitored during an acute decompensation in patients with severe liver dysfunction.

5.12. Medication and supplement considerations

Patients and/or their families should be encouraged to notify their medical providers and pharmacies of all medications and supplements to monitor for any potential drug interactions or medications contraindicated due to their condition.

In individuals with hepatic disease, particularly those with hepatic insufficiency, hepatotoxic medications and supplements should be avoided. Alcohol should not be consumed and commonly used medications for teenage patients, including vitamin A derivative-containing acne medications and estrogen-containing oral contraceptives, should be avoided. Other common medications known to cause drug-induced liver injury are acetaminophen, antibiotics (minocycline, rifampin, isoniazid, rifampin, amoxicillin/clavulanic acid), antiepileptic drugs (valproates), and chemotherapy agents (methotrexate, asparaginase, etc.). When necessary, liver function tests should be closely monitored. Considerations for parenteral nutrition composition are included in Section 5.11. In patients with advanced liver dysfunction, the dose of benzodiazepines needs to be minimized due to impaired hepatic clearance. Medications impairing blood coagulation (i.e., Warfarin, non-steroidal anti-inflammatory drugs, and aspirin) should be avoided in

patients with portal hypertension with thrombocytopenia and esophageal varices. For patients with a history of hypoglycemia and/or elevated ketones, β -blockers should be used with caution due to their potential to mask symptoms of hypoglycemia. For patients who have received a liver transplant, choice of steroids and immunosuppressants need careful consideration as steroid- and tacrolimus-induced hypertension can cause deterioration of heart function.

In individuals with neuromuscular involvement, potentially myotoxic medications, including statins, antipsychotic medications, antidepressants, neuroleptics, and certain general anesthetic agents should be used with caution and with close monitoring with laboratory studies, particularly ALT, AST, and CK. Patients taking these medications should be instructed to inform their medical provider immediately or seek urgent medical attention if they develop any signs of rhabdomyolysis, including muscle pain/cramps, spasms, or darkening of urine. Medications that affect muscle strength, i.e., muscle relaxers, should also be used in caution in individuals with muscular involvement. In individuals with significant cardiac disease, medications that may affect cardiac function/rhythm should be prescribed in consultation with a pharmacist and/or cardiologist. Limited evidence on specific surgical and anesthesia considerations for GSD IV, including APBD, is available [192], and an anesthesiologist, ideally one familiar with metabolic disorders, should be consulted prior to any surgery.

5.13. Additional medical considerations

All patients with GSD IV, including APBD, should have a primary care physician (PCP) who is familiar with the disease and comfortable communicating with the other providers on the patient care team. The PCP should manage any non-GSD IV related medical issues and illnesses, perform routine physical examinations, and provide appropriate immunizations to the patient. Routine immunizations should be provided to the patient by the PCP as recommended by the Centers for Disease Control and Prevention (CDC) (<http://www.cdc.gov/vaccines/recs/schedules/default.htm>). Of particular importance, Hepatitis A and B vaccinations should be provided to the patient, given the significant risk of liver disease in this patient population. All adult patients with GSD IV, including APBD, are advised to receive a hepatitis titer test that includes immunity testing for Hepatitis A and B. Live vaccines of mumps, measles, rubella, and varicella-zoster (MMRV) are recommended as soon as age-applicable (and prior to liver transplantation) because they are contraindicated post-liver transplantation.

Age-matched height and weight and weight/height ratio should be monitored closely. Alternative methods of measurement of height/recumbent length may be indicated in individuals with contractures; segmental measurements, including upper arm length, ulnar length, knee height, and tibial length, are used as proxy measurements for height/recumbent length in individuals with other neuromuscular conditions, such as cerebral palsy and Duchenne muscular dystrophy, and can be used as necessary in individuals in whom accurate height/length measurements cannot otherwise be obtained [170]. For children, the PCP should also monitor childhood development and achievement of developmental milestones, particularly in individuals with musculoskeletal involvement. Changes in growth trends should be evaluated carefully as this may indicate nutritional deficiencies (insufficient caloric or protein intake, deficiencies of nutrients including fat-soluble vitamins) or worsening of disease state, particularly for cirrhosis in children with hepatic GSD IV.

Good dental hygiene and frequent monitoring of dental health by a dentist should also be encouraged, particularly in individuals with cardiac disease. Annual vision exams should be performed to screen for changes in vision or dysfunction related to neuro-ophthalmologic involvement. Patients can wear a medical alert bracelet to alert others to their diagnosis if need arises. Monitoring of bone density with X-ray-based bone density scans (DEXA, DXA) are recommended, particularly for individuals with myopathy. In addition to risk for repeat

hospitalizations for pressure wounds and UTI in APBD, hospitalizations due to aspiration pneumonia and related complications are common, and patients should be routinely screened for dysphagia given the risk of silent aspiration and subsequent infection.

During times of surgery, infections, or other intercurrent illnesses, the patient's metabolic genetics clinic should be contacted in advance to provide management recommendations. There is theoretical concern that pregnancy could cause unmasking of neuromuscular and motor manifestations in GSD IV, including APBD (e.g., weakness during labor), though there have been no reports of obstetric concerns in these populations. There has also been no report of GSD IV-related impact on renal or hematologic function.

ADDITIONAL MEDICAL RECOMMENDATIONS

- All individuals with GSD IV, including APBD, should have a PCP.
 - Routine immunizations should be given as recommended by the CDC.
 - Hepatitis A and B vaccinations should be provided to all individuals affected by GSD IV, including APBD, given the risk of liver disease. Adult patients are advised to receive a hepatitis titer test.
 - Age-matched height and weight and weight/height ratio should be monitored closely.
 - Good dental hygiene and routine dental health monitoring is advised.
 - Annual vision exams should be performed to screen for vision changes or dysfunction.
 - Monitoring of bone density is recommended, particularly for individuals with myopathy.
 - Individuals with APBD should be routinely screened for dysphagia given the risk of silent aspiration and subsequent infection.
-

6. Research and community resources

Resources are available to support affected individuals, medical professionals, and researchers (Table 4).

7. Knowledge gaps and future research directions

Multiple GSD IV cell and animal models have been developed and discovered which facilitate understanding of GSD IV natural history as well as the potential of preclinical management and therapeutic techniques. Details on each model are included in the Supplementary Material S1.

The prevalence of dysautonomia in GSD IV, particularly in APBD, is not well understood. APBD patients have anecdotally reported signs and symptoms of autonomic dysfunction including orthostatic hypotension, drops in blood pressure, rapid changes in body temperature, and distal edema, yet these signs remain underreported [85,92,171]; additional research on the prevalence of dysautonomia in APBD is needed. Similarly, the impact of polyglucosan body deposition on vision quality requires further research. Anecdotally and briefly in the literature [7,152–155], complaints of vision loss or vision dysfunction has been reported. Research into the mechanisms responsible for the vision alterations, such as optic nerve atrophy or occlusion, is warranted. Moreover, reports of chronic and progressive pain have been noted in APBD, and additional research is needed to understand the pathology so that appropriate management and treatment techniques can be applied. Lastly, it is unclear if there are specific nephrology or hematology considerations for GSD IV. Limited reports of reticuloendothelial system (RES) involvement have been noted in those patients with GSD IV and primarily hepatic involvement [88]; additional research into the prevalence of RES in GSD IV is warranted. Additional natural history research is critical to better understand the disease progression and clinical spectrum of GSD IV, including APBD. Research on the mechanisms responsible for the neurologic, urologic, autonomic, and gastrointestinal manifestations, as well as the potential of dietary therapy, is needed.

The extent to which glucose metabolism and/or blood glucose control is altered in GSD IV, including APBD, is unclear. Additional research

Table 4

Useful research and community resources for individuals affected by glycogen storage disease type IV (GSD IV), including the adult-onset form adult polyglucosan body disease (APBD), as well as medical professionals and researchers.

Resource	Title	Description/Website
Natural history studies, patient registries, and biorepositories	GBE Deficiency (GSD IV and APBD) Natural History Study	A repository of clinical, laboratory, and biochemical information on individuals with GSD IV, including APBD. This information will allow a more definitive description of GBE deficiency to be developed, which will permit development of treatment strategies for this disease. http://clinicaltrials.gov/ct2/show/NCT02683512
	Columbia University APBD Registry (CAP)	The APBD registry is a database designed to store medical and contact information about patients with APBD, as well as their family members.
	Myelin Disorders Biorepository Project (MDBP)	The MDBP collects and analyzes clinical data and biological samples from leukodystrophy patients worldwide to support ongoing and future research projects. http://clinicaltrials.gov/ct2/show/NCT03047369
Websites*	APBD Research Foundation	http://www.apbdrf.org
	Association for Glycogen Storage Disease (AGSD)	http://www.agsdus.org
	National Organization for Rare Disorders (NORD)	http://www.rarediseases.org
	Association for Glycogen Storage Disease-United Kingdom (AGSD-UK)	http://www.agsd.org.uk
	Genetic and Rare Diseases (GARD) Information Center	http://rarediseases.info.nih.gov/
News Releases	Metabolic Support UK	http://www.metabolicsupportuk.org
	APBD Patient-Led Listening Session with the Food and Drug Administration (FDA)	http://www.apbdrf.org/wp-content/uploads/2021/11/FDA-listening-Session-Summary-FINAL.pdf
Conferences	International Glycogen Storage Disease Annual Conference	http://www.agsdus.org
	Annual AGSD Conference	http://www.agsdus.org
	Annual APBD Scientific & Community Conference	http://www.apbdrf.org

The list was updated in December 2022 and is not considered to be comprehensive.

* Some GSD support groups offer social media groups in their local languages.

on mechanisms that could cause dysregulation of glucose metabolism is needed and should include: (1) the extent to which polyglucosan accumulation and/or reduction of GBE activity compromises cell functionality and/or capacity to synthesize glycogen (polyglucosan) efficiently, (2) the efficiency to which glycogenolytic enzymes can access and degrade polyglucosan, and (3) the impact of polyglucosan accumulation on hepatocyte ability to mobilize and release free glucose to maintain euglycemia. Additionally, researchers should consider the extent to which proteolysis could compensate for reductions in available glucose in the liver by upregulating gluconeogenesis, particularly in individuals with muscular involvement in which myopathy could induce catabolic proteolysis.

The role of neuroinflammation in the underlying pathogenesis of APBD is not fully elucidated. Given the lack of blood-brain barrier breakdown evident on MRI and neuropathology, it is not likely that invading peripheral immune cells play a significant role in CNS and PNS damage. Instead, neuroinflammation in APBD is most likely “compartmentalized” [172] within the nervous systems – mediated by Schwann cells in the PNS and microglia and astrocytes in the CNS. Neuropathology of APBD shows that polyglucosan bodies accumulate in axons, as well as inside astrocyte [144,145,155] and Schwann cell [69] processes. In the healthy brain, astrocytes are a significant source of glycogen and provide metabolic substrates to neurons, myelinated axons, and oligodendrocytes (the cells that make myelin) [173]. The diffuse white matter damage identified on brain MRI in APBD [27] likely reflects disruption of this pathway, causing oligodendrocyte and myelin loss [155] leading to axonal degeneration [174] (Supplementary Fig. S1); however, the “reactive” astrocyte response in APBD needs to be better defined [175]. Microglia, the innate immune cells of the brain [176], should participate in both short- and long-term response to white matter damage to oligodendrocytes, axons, and astrocytes (perhaps similar to MS pathology [177]); this requires further investigation in APBD. As an initial step to better understand when and how white matter damage occurs in APBD, it is recommended to obtain a brain MRI to identify presence of white matter lesions, and to perform surveillance brain MRIs to determine progression over time. Additional research on the effect of altered glucose metabolism on the CNS and PNS in the setting of GSD IV is needed.

In light of the enzyme and gene replacement strategies that are either approved or under active development for other subtypes of GSDs and other neuromuscular diseases, it is scientifically feasible to develop similar therapies for GSD IV and perform preclinical testing on cellular and animal models of the disease. Restoration of GBE activity and the GBE/GYS ratio are considered to be valuable indicators of disease correction and are desired therapeutic strategies. Alternative therapies including those that decrease glycogen synthesis by reducing GYS activity or increasing lysosomal glycogen degradation are potential avenues for preventing, or possibly even reversing, disease progression [178,179,193]. Additional investigations in the GSD IV mouse and patient cell models are evaluating the efficacy of antisense oligosaccharides for correcting *GBE1* mutations and the potential of gene therapy to restore GBE activity [180]. Lastly, small molecules including guaiacol (a GYS inhibitor) and 144DG11 (a facilitator of auto-lysosomal glycogen degradation through enhanced autophagy) are being investigated for their function in reducing polyglucosan [181,182].

Despite the advancements in various treatment approaches, a sensitive and specific biomarker of disease progression (or regression) has not been identified in patients with GSD IV. Diffuse reticuloendothelial injury can be observed in patients with hepatic and neuromuscular involvement, and raised chitotriosidase is a non-specific marker that is often seen in chronic liver diseases with macrophage activation; there are previous reports of children with GSD IV who had high chitotriosidase levels [63,183,184]. Urinary glucose tetrasaccharide (Glc4, also referred to as Hex4) excretions have been studied in several GSD types. Glc4 is a degradation product of glycogen and other similar branched chain starches, such as amylopectin, and it is synthesized by the glycolytic activity of salivary and pancreatic α -amylases and neutral α -1,4-glucosidase activities [185,186]. Glc4 is associated with increased glycogen storage in both liver and muscle [186–188], and has been proposed as a marker of metabolic control in GSD IV, including APBD. The utility of urine Glc4 in GSD IV is unclear, with reports finding both normal and elevated Glc4 concentrations in patients with GSD IV [189]. Therefore, long-term systematic studies are needed.

Ideally, a serum or plasma biomarker as well as a noninvasive tool to monitor polyglucosan bodies or glycogen content would be identified to

monitor disease progression or treatment success. Translation to human clinical trials will present a challenge due to the ultra-rare occurrence of the disease. Primary outcome measures for such clinical trials may include length of survival and the need for mechanical ventilation. Novel biostatistical approaches to help conduct rigorous analyses of small cohorts and evolution of FDA clinical trial requirements for ultra-rare diseases will help translate novel therapies into the clinic in the future. Several other diseases, including GSD types VII (Tarui disease) and XV (polyglucosan body myopathy type 2), RBCK1 deficiency (polyglucosan body myopathy 1), PRKAG2 syndrome, Danon disease, and Lafora disease, are caused by accumulation of poorly branched glycogen or polyglucosan accumulation, and therefore will likely benefit from similar treatment approaches and biomarker development.

8. Conclusion

GSD IV is an ultra-rare autosomal recessive disease caused by variants in *GBE1* which results in reduced or deficient GBE activity. GSD IV is a clinically heterogeneous disorder associated with a range of hepatic, neurologic, muscular, and/or cardiac manifestations that may present in utero, during infancy, childhood, or adolescence, as well as in middle to late adulthood as APBD. Diagnosis of GSD IV at any point in the lifespan is established through identification of biallelic pathogenic variants in *GBE1*. If molecular testing is inconclusive, reduction or deficiency of GBE activity through enzymology, in conjunction with clinical presentation consistent with the disease, will confirm the diagnosis. Tissue biopsy typically reveals PAS-positive cellular inclusions that are resistant or partially-resistant to diastase (polyglucosan), though these histological findings are not sufficient for diagnosis. Tissue selection for biopsy should be based on presenting symptoms and suspected affected tissue. Longitudinal, multidisciplinary follow-up is essential for all patients, regardless of age, and should include experts in medical genetics, hepatology, neurology, physical rehabilitation, cardiology, behavioral psychology, urology, and nutrition.

Disclosures

AA, SLA, DSB, TAB, LEC, MH, PBK, BTK, RLK, PSK, APL, JLO-M, SP, ALS, CS-A, and RS have no relevant disclosures. HOA has received research funding from The Keith B. Hayes Foundation for investigating polyglucosan diseases. DSG serves on the Executive Board of the APBD Research Foundation. Funding of this resource was provided in part by the Association for Glycogen Storage Disease that was restricted to the use of developing this clinical practice resource.

Data availability

No data was used for the research described in the article.

Acknowledgments

The authors gratefully acknowledge the patients and caregivers who have served as “patient advocates” and provided input for the development of this resource, as well as the Association for Glycogen Storage Disease and the Adult Polyglucosan Body Disease Research Foundation for their critical review and suggestions. The authors also acknowledge Dr. Ghada Hijazi, Leticia Flores, and Jenna Foltz for their assistance with the creation of this resource, and Erica Nading and Dr. Jordan Foreman for their review. Figs. 1 and 2 were created with [BioRender.com](https://www.biorender.com).

Appendix A. Supplementary Data

Supplementary material to this article can be found online at <https://doi.org/10.1016/j.jmgme.2023.107525>.

References

- [1] R.V. Stick, S.J. Williams, Chapter 9 - disaccharides, oligosaccharides and polysaccharides, in: R.V. Stick, S.J. Williams (Eds.), *Carbohydrates: The Essential Molecules of Life* (Second Edition), Elsevier, Oxford 2009, pp. 321–341.
- [2] G. Cenacchi, V. Papa, R. Costa, V. Pegoraro, R. Marozzo, M. Fanin, C. Angelini, Update on polyglucosan storage diseases, *Virchows Arch.* 475 (2019) 671–686.
- [3] D. Sean Froese, A. Michaeli, T.J. McCorvie, T. Krojer, M. Sasi, E. Melaev, A. Goldblum, M. Zatzepin, A. Lossos, R. Álvarez, P.V. Escribá, B.A. Minassian, F. Von Delft, O. Kakhlon, W.W. Yue, Structural basis of glycogen branching enzyme deficiency and pharmacologic rescue by rational peptide design, *Hum. Mol. Genet.* 24 (2015) 5667–5676.
- [4] M.A. Sullivan, S. Nitschke, M. Steup, B.A. Minassian, F. Nitschke, Pathogenesis of Lafora disease: transition of soluble glycogen to insoluble Polyglucosan, *Int. J. Mol. Sci.* 18 (2017) 1743.
- [5] F. Nitschke, P. Wang, P. Schmieder, J.-M. Girard, Donald E. Awrey, T. Wang, J. Israelian, X. Zhao, J. Turnbull, M. Heydenreich, E. Kleinpeter, M. Steup, Berge A. Minassian, Hyperphosphorylation of Glucosyl C6 carbons and altered structure of glycogen in the neurodegenerative epilepsy Lafora disease, *Cell Metab.* 17 (2013) 756–767.
- [6] M.A. Sullivan, S. Nitschke, E.P. Skwara, P. Wang, X. Zhao, X.S. Pan, E.E. Chown, T. Wang, A.M. Perri, J.P.Y. Lee, F. Vilaplana, B.A. Minassian, F. Nitschke, Skeletal Muscle Glycogen Chain Length Correlates with Insolubility in Mouse Models of Polyglucosan-Associated Neurodegenerative Diseases, *Cell Reports*, Elsevier B.V., 2019 1334–1344.e1336.
- [7] Y. Robitaille, S. Carpenter, G. Karpati, S.D. DiMauro, A distinct form of adult polyglucosan body disease with massive involvement of central and peripheral neuronal processes and astrocytes: a report of four cases and a review of the occurrence of polyglucosan bodies in other conditions such as Lafora's disease and normal ageing, *Brain* 103 (1980) 315–336.
- [8] P.L. Magoulas, A.W. El-Hattab, Glycogen storage disease type IV, in: M.P. Adam, H.H. Ardinger, R.A. Pagon, S.E. Wallace, L.J.H. Bean, K. Stephens, A. Amemiya (Eds.), *GeneReviews*(®), University of Washington, Seattle Copyright © 1993–2020, University of Washington, Seattle. *GeneReviews* Is a Registered Trademark of the University of Washington, Seattle. All rights reserved, Seattle (WA), 1993.
- [9] MedlinePlus, Adult Polyglucosan Body Disease, National Library of Medicine, Bethesda (MD): National Library of Medicine (US), 2022.
- [10] L.R. Schwartz, Q. Lu, R. Liu, R. Kornreich, L.L. Edelman, A.H. Birch, A. Lossos, O. Kakhlon, O.H. Akman, Estimating the prevalence of the adult polyglucosan body disease at the gene level for Ashkenazi Jews in the United States American, *J. Rare Disord.: Diagn. Ther.* 3 (2020) 4–8.
- [11] D.H. Andersen, in: V.A. Najjar (Ed.), *Carbohydrate Metabolism*, Johns Hopkins Press, Baltimore 1952, p. 28.
- [12] D.H. Andersen, Familial cirrhosis of the liver with storage of abnormal glycogen., *Laboratory investigation, J. Tech. Methods Pathol.* (1956) 11–20.
- [13] J.B. Sidbury Jr., J. Mason, W.B. Burns Jr., B.H. Ruebner, Type IV Glycogenosis. Report of a Case Proven by Characterization of Glycogen and Studied at Necropsy Bulletin of the Johns Hopkins Hospital, 111, 1962 157–181.
- [14] L.W. Hollman, J.A. van der Haar, G.A. de Vaan, Type IV Glycogenosis Laboratory Investigation, 15, 1966 357–367.
- [15] B.I. Brown, D.H. Brown, Lack of an alpha-1,4-glucan: alpha-1,4-glucan 6-glycosyl transferase in a case of type IV glycogenosis, *Proceedings of the National Academy of Sciences of the United States of America*, 56, 1966, pp. 725–729.
- [16] E. Reusche, F. Aksu, H.H. Goebel, Y.S. Shin, T. Yokota, H. Reichmann, A mild juvenile variant of type IV glycogenosis, *Brain and Development* (1992) 36–43.
- [17] S. Servidei, R.E. Riepe, C. Langston, L.Y. Tani, J.T. Bricker, N. Crisp-Lindgren, H. Travers, D. Armstrong, S. DiMauro, Severe cardiopathy in branching enzyme deficiency, the journal of pediatrics, *J. Pediatr.* (1987) 51–56.
- [18] J.M. Schröder, R. May, Y.S. Shin, M. Sigmund, S. Nase-Hüppmeier, Juvenile hereditary polyglucosan body disease with complete branching enzyme deficiency (type IV glycogenosis), *Acta Neuropathol.* 85 (1993) 419–430.
- [19] I.T. Ferguson, M. Mahon, W.J.K. Cumming, An adult case of Andersen's disease - type IV glycogenosis. A clinical, histochemical, ultrastructural and biochemical study, *J. Neurol. Sci.* 60 (1983) 337–351.
- [20] T.T. Tang, A.D. Segura, Y.T. Chen, L.M. Ricci, R.A. Franciosi, M.L. Splaingard, M.S. Lubinsky, Neonatal hypotonia and cardiomyopathy secondary to type IV glycogenosis, *Acta Neuropathol.* 87 (1994) 531–536.
- [21] G. Van Noort, W. Straks, O.P. Van Diggelen, R.C.M. Hennekam, A congenital variant of glycogenosis type IV, *Pediatr. Pathol.* 13 (1993) 685–698.
- [22] H.L. Greene, B.I. Brown, D.T. McClenathan, R.M. Agostini Jr., S.R. Taylor, A New Variant of Type IV Glycogenosis: Deficiency of Branching Enzyme Activity without Apparent Progressive Liver Disease *Hepatology* (Baltimore, Md.), vol. 8, 1988 302–306.
- [23] A. McConkie-Rosell, C. Wilson, D.A. Piccoli, J. Boyle, T. DeClue, P. Kishnani, J.J. Shen, A. Boney, B. Brown, Y.T. Chen, Clinical and laboratory findings in four patients with the non-progressive hepatic form of type IV glycogen storage disease, *J. Inher. Metab. Dis.* 19 (1996) 51–58.
- [24] J.F. Pellissier, T. de Bary, J. Bille, G. Serratrice, M. Toga, Polysaccharide (amylopectin-like) storage myopathy histochemical, *Ultrastruct. Biochem. Stud.* (1981) 292–296.
- [25] A. Lossos, V. Barash, D. Soffer, Z. Argov, M. Gomori, Z. Ben-Nariah, O. Abramsky, I. Steiner, Hereditary branching enzyme dysfunction in adult polyglucosan body disease: a possible metabolic cause in two patients, *Ann. Neurol.* 30 (1991) 655–662.
- [26] H.O. Akman, A. Lossos, O. Kakhlon, *GBE1 Adult Polyglucosan Body Disease*, University of Washington, Seattle, Seattle (WA), *GeneReviews*, 2020.

- [27] F. Moche, R. Schiffmann, M.E. Steenweg, H.O. Akman, M. Wallace, F. Sedel, P. Laforêt, R. Levy, J.M. Powers, S. Demeret, T. Maisonne, R. Froissart, B.B. Da Nobrega, B.L. Fogel, M.R. Natowicz, C. Lubetzk, A. Durr, A. Brice, H. Rosenmann, V. Barash, O. Kakhlon, J.M. Gomori, M.S. van der Knaap, A. Lossos, Adult polyglucosan body disease: natural history and key magnetic resonance imaging findings, *Ann. Neurol.* 72 (2012) 433–441.
- [28] R. Schiffmann, M.E. Wallace, D. Rinaldi, I. Ledoux, M.P. Luton, S. Coleman, H.O. Akman, K. Martin, J.Y. Hogrel, D. Blankenship, J. Turner, F. Moche, A double-blind, placebo-controlled trial of triheptanoin in adult polyglucosan body disease and open-label, long-term outcome, *J. Inherit. Metab. Dis.* 41 (2018) 877–883.
- [29] B.T. Kiely, R.L. Koch, L. Flores, D. Burner, S. Kaplan, P.S. Kishnani, A novel approach to characterize phenotypic variation in GSD IV: Reconceptualizing the clinical continuum, *Front. Genet.* 13 (2022).
- [30] K. Lee, T. Ernst, G. Løhaugen, X. Zhang, L. Chang, Neural correlates of adaptive working memory training in a glycogen storage disease type-IV patient annals of clinical and translational, *Neurology* 4 (2017) 217–222.
- [31] A. Lossos, C.J. Klein, K.M. McEvoy, B.M. Keegan, A 63-year-old woman with urinary incontinence and progressive gait disorder, *Neurology* 72 (2009) 1607–1613.
- [32] M.A. Hellmann, O. Kakhlon, E.H. Landau, M. Sadeh, N. Giladi, I. Schlesinger, D. Kidron, O. Abramsky, A. Reches, Z. Argov, J.M. Rabey, J. Chapman, H. Rosenmann, A. Gal, J. Moshe Gomori, V. Weiner, A. Lossos, Frequent misdiagnosis of adult polyglucosan body disease, *J. Neurol.* 262 (2015) 2346–2351.
- [33] C. Paradas, H.O. Akman, C. Ionete, H. Lau, P.N. Riskind, D.E. Jones, T.W. Smith, M. Hirano, S. Dimauro, Branching enzyme deficiency: expanding the clinical spectrum, *JAMA Neurol.* 71 (2014) 41–47.
- [34] D. Shprecher, J. Schwalb, R. Kurlan, Normal pressure hydrocephalus: diagnosis and treatment, *Curr. Neurol. Neurosci. Rep.* 8 (2008) 371–376.
- [35] T. Aksu, A. Colak, O. Tufekcioglu, Cardiac involvement in glycogen storage disease type IV: two cases and the two ends of a Spectrum, *Case Rep. Med.* 2012 (2012), 764286.
- [36] I.K. Onal, N. Turhan, E. Oztas, M. Arhan, Z. Akcoren, P. Oguz, M. Akdogan, E.D. Onal, S. Kacar, M. Kurt, N. Sasmaz, Hepatocellular carcinoma in an adult patient with type IV glycogen storage disease, *Acta Gastro-Enterol. Belgica* 72 (2009) 377–378.
- [37] H. Ozen, Glycogen storage diseases: new perspectives, *World J. Gastroenterol.* 13 (2007) 2541–2553.
- [38] S.C. Li, C.M. Chen, J.L. Goldstein, J.Y. Wu, E. Lemyre, T.A. Burrow, P.B. Kang, Y.T. Chen, D.S. Bali, Glycogen storage disease type IV: Novel mutations and molecular characterization of a heterogeneous disorder, *J. Inherit. Metab. Dis.* 33 (2010) Suppl 3:S83–90.
- [39] S. Yao, X.-K. Qi, B. Xiong, W. Zhang, R.-L. Zheng, Y. Yuan, The clinical and pathological characteristics of a patient with glycogen storage disease IV, *Zhonghua nei ke za zhi [Chin. J. Int. Med.]* 48 (2009) 380–382.
- [40] T.G.J. Derks, F. Peeks, F. de Boer, M. Fokkert-Wilts, H.P.J. van der Doef, M.C. van den Heuvel, E. Szymanska, D. Rokicki, P.T. Ryan, D.A. Weinstein, The potential of dietary treatment in patients with glycogen storage disease type IV, *J. Inherit. Metab. Dis.* 44 (2021) 693–704.
- [41] K. Ichimoto, T. Fujisawa, M. Shimura, T. Fushimi, M. Tajika, A. Matsunaga, M. Ogawa-Tominaga, N. Akiyama, Y. Naruke, H. Horie, T. Fukuda, H. Sugie, A. Inui, K. Murayama, Two cases of a non-progressive hepatic form of glycogen storage disease type IV with atypical liver pathology, *Mol. Genet. Metabol. Rep.* 24 (2020).
- [42] H. Iijima, R. Iwano, Y. Tanaka, K. Muroya, T. Fukuda, H. Sugie, K. Kurosawa, M. Adachi, Analysis of GBE1 mutations via protein expression studies in glycogen storage disease type IV: A report on a non-progressive form with a literature review, *Mol. Genet. Metabol. Rep.* 17 (2018) 31–37.
- [43] M. Liu, L.-Y. Sun, Liver transplantation for glycogen storage disease type IV, *Front. Pediatr.* 9 (2021) 633822.
- [44] S.M. Said, M.J. Murphree, T. Mounajjed, M. El-Youssef, L. Zhang, A Novel GBE1 Gene Variant in a Child with Glycogen Storage Disease Type IV, *Human Pathology*, W.B. Saunders, 2016 152–156.
- [45] A. Wei, H. Ma, Z. Li, L. Zhang, R. Zhang, T. Wang, Type IV glycogen storage disease associated with Hemophagocytic Lymphohistiocytosis: a Case report, *J. Pediatr. Hematol. Oncol.* 42 (2020) 368–369.
- [46] N. Afdhal, J. McHutchison, R. Brown, I. Jacobson, M. Manns, F. Poordad, B. Weksler, R. Esteban, Thrombocytopenia associated with chronic liver disease, *J. Hepatol.* 48 (2008) 1000–1007.
- [47] S. Pan, S. Zhu, M. Yu, Clinical characteristics and gene mutation analysis of one pedigree with glycogen storage disease type IV, *Biomed. Res. (India)* 29 (2018) 2160–2163.
- [48] R.A. de Moor, J.J. Schweizer, B. van Hoek, M. Wasser, R. Vink, P.D. Maaswinkel-Mooy, Hepatocellular carcinoma in glycogen storage disease type IV, *Arch. Dis. Child.* 82 (2000) 479–480.
- [49] W. Yu, M.A. Brundler, J.R. Wright, Polyglucosan Bodies in Placental Extravillous Trophoblast for the Diagnosis of Fetal Perinatal Neuromuscular-Type Glycogen Storage Disease Type IV, *Pediatric and Developmental Pathology*, SAGE Publications Ltd, 2018 423–427.
- [50] H.O. Akman, C. Karadimas, Y. Gyftodimou, M. Grigoriadou, H. Kokotas, A. Konstantinidou, H. Anninos, E. Patsouris, H.M. Thaker, J.B. Kaplan, I. Besharat, K. Hatzikonstantinou, S. Fotopoulos, S. DiMauro, M.B. Petersen, Prenatal diagnosis of glycogen storage disease type IV, *Prenat. Diagn.* 26 (2006) 951–955.
- [51] C. Bruno, O.P. Van Diggelen, D. Cassandrini, M. Gimpelev, B. Giuffrè, M.A. Donati, P. Introvin, A. Alegria, S. Assereto, L. Morandi, M. Mora, E. Tonoli, S. Mascelli, M. Traverso, E. Pasquini, M. Bado, L. Vilarinho, G. Van Noort, F. Mosca, S. DiMauro, F. Zara, C. Minetti, Clinical and genetic heterogeneity of branching enzyme deficiency (glycogenosis type IV), *Neurology* 63 (2004) 1053–1058.
- [52] B. Giuffrè, R. Parini, T. Rizzuti, L. Morandi, O.P. van Diggelen, C. Bruno, M. Giuffrè, G. Corsello, F. Mosca, Severe neonatal onset of glycogenosis type IV: clinical and laboratory findings leading to diagnosis in two siblings, *J. Inherit. Metab. Dis.* 27 (2004) 609–620.
- [53] C. Lamperti, S. Salani, S. Lucchiar, A. Bordini, M. Ripolone, G. Fagiolari, M.E. Fruguglietti, V. Crugnola, C. Colombo, A. Cappellini, A. Prella, N. Bresolin, G.P. Comi, M. Moggio, Neuropathological study of skeletal muscle, heart, liver, and brain in a neonatal form of glycogen storage disease type IV associated with a new mutation in GBE1 gene, *J. Inherit. Metab. Dis.* 32 (2009).
- [54] S.C. Li, W.L. Hwu, J.L. Lin, D.S. Bali, C. Yang, S.M. Chu, Y.H. Chien, H.C. Chou, C.Y. Chen, W.S. Hsieh, P.N. Tsao, Y.T. Chen, N.C. Lee, Association of the congenital neuromuscular form of glycogen storage disease type IV with a large deletion and recurrent frameshift mutation, *Journal of child neurology*, *J. Child Neurol.* (2012) 204–208.
- [55] M.K. Herrick, J.L. Twiss, G.D. Vladutiu, G.F. Glasscock, D.S. Horoupian, Concomitant branching enzyme and phosphatase deficiencies. An unusual glycogenosis with extensive neuronal polyglucosan storage, *J. Neuropathol. Exp. Neurol.* 53 (1994) 239–246.
- [56] K. Maruyama, T. Suzuki, T. Koizumi, H. Sugie, T. Fukuda, M. Ito, J. Hirato, Congenital form of glycogen storage disease type IV: a case report and a review of the literature, *Pediatr. Int.* 46 (2004) 474–477.
- [57] A.R. Jancke, S. Dertinger, U.P. Ketelsen, L. Bereuter, B. Simma, T. Müller, W. Vogel, F.A. Offner, Neonatal type IV glycogen storage disease associated with “null” mutations in glycogen branching enzyme 1, *J. Pediatr.* 145 (2004) 705–709.
- [58] M. Nambu, K. Kawabe, T. Fukuda, T.B. Okuno, S. Ohta, I. Nonaka, H. Sugie, I. Nishino, A neonatal form of glycogen storage disease type IV, *Neurology* 61 (2003) 392–394.
- [59] K.W. Nolte, A.R. Jancke, M. Vorgerd, J. Weis, J.M. Schröder, Congenital type IV glycogenosis: the spectrum of pleomorphic polyglucosan bodies in muscle, nerve, and spinal cord with two novel mutations in the GBE1 gene, *Acta Neuropathol.* 116 (2008) 491–506.
- [60] P.G. Raju, H.C. Li, D.S. Bali, Y.T. Chen, D.K. Urion, H.G.W. Lidov, P.B. Kang, A case of congenital glycogen storage disease type IV with a novel GBE1 mutation, *J. Child Neurol.* 23 (2008) 349–352.
- [61] A.L. Taratuto, H.O. Akman, M. Saccoliti, M. Riudavets, N. Arakaki, L. Mesa, G. Seveler, H. Goebel, S. DiMauro, Branching enzyme deficiency/glycogenosis storage disease type IV presenting as a severe congenital hypotonia: muscle biopsy and autopsy findings, biochemical and molecular genetic studies, *Neuromuscul. Disord.* 20 (2010) 783–790.
- [62] C.N. Massey, D. Dannaway, Glycogen storage disease type IV: Clinical presentation and diagnosis in a neonate, *J. Investig. Med.* 67 (2019) 524.
- [63] A. Schänzer, D. Faas, S. Rust, T. Podskarbi, A.B.P. Van Kuilenburg, M. Scarpa, A. Kunze, T. Marquardt, A. Hahn, Distinctly elevated Chitotriosidase activity in a child with congenital Andersen disease (glycogen storage disease type IV), *Klin. Padiatr.* 228 (2016) 277–279.
- [64] C. Fernandez, C. Halbert, A.M. De Paula, V. Lacroze, R. Froissart, D. Figarella-Branger, B. Chabrol, J.F. Pellissier, Non-lethal neonatal neuromuscular variant of glycogenosis type IV with novel GBE1 mutations, *Muscle Nerve* 41 (2010) 269–271.
- [65] J. Fernandes, F. Huijting, Branching enzyme-deficiency glycogenosis: studies in therapy, *Arch. Dis. Child.* 43 (1968) 347–352.
- [66] I.F. Schene, C.G. Korenke, H.H. Huidekoper, L. van der Pol, D. Dooijes, J.M.P.J. Breur, S. Biskup, S.A. Fuchs, G. Visser, Glycogen storage disease type IV: a rare cause for neuromuscular disorders or often missed? *J. Inherited Metab. Dis. Rep.* 45 (2019) 99–104.
- [67] C.J. Klein, C.J. Boes, J.E. Chapin, C.D. Lynch, N.G. Campeau, P.J.B. Dyck, P.J. Dyck, Adult polyglucosan body disease: Case description of an expanding genetic and clinical syndrome, *Muscle Nerve* 29 (2004) 323–328.
- [68] R. Phadke, E. Murphy, O. Ciccarelli, M. Koltzenburg, R. Kirk, M. Lunn, Unusual demyelinating pathology in a case of adult polyglucosan body disease, *Neuromuscul. Disord.* 25 (2015) S222.
- [69] S. Sampaolo, T. Esposito, F. Gianfrancesco, F. Napolitano, L. Lombardi, R. Lucà, F. Roperto, G. Di Iorio, A novel GBE1 mutation and features of polyglucosan bodies autophagy in adult polyglucosan body disease, *Neuromuscul. Disord.* 25 (2015) 247–252.
- [70] E.E. Ubogu, S.T.K. Hong, H.O. Akman, S. Dimauro, B. Katirji, D.C. Preston, B.E. Shapiro, Adult polyglucosan body disease: a case report of a manifesting heterozygote, *Muscle Nerve* 32 (2005) 675–681.
- [71] S.W. Moses, R. Parvari, The variable presentations of glycogen storage disease type IV: a review of clinical, enzymatic and molecular studies, *Curr. Mol. Med.* 2 (2002) 177–188.
- [72] P. Rosenthal, L. Podesta, R. Grier, J.W. Said, L. Sher, J. Cocjin, F. Watanabe, E. Vasilias, R. Van De Velde, L. Makowka, Failure of liver transplantation to diminish cardiac deposits of amyloidosis and leukocyte inclusions in type iv glycogen storage disease, *Liver Transpl. Surg.* (1995) 373–376.
- [73] C. Bruno, D. Cassandrini, S. Assereto, H. Orhan Akman, C. Minetti, S. Di Mauro, Neuromuscular forms of glycogen branching enzyme deficiency, *Acta Myolog.* 26 (2007) 75–78.
- [74] A. Lossos, Z. Weiner, V. Barash, D. Soffer, I. Schlesinger, O. Abramsky, Z. Argov, S. Shpitzen, V. Weiner, Adult polyglucosan body disease in Ashkenazi Jewish patients carrying the Tyr329Ser mutation in the glycogen-branching enzyme gene, *Ann. Neurol.* 44 (1998) 867–872.
- [75] H.O. Akman, O. Kakhlon, J. Coku, L. Peverelli, H. Rosenmann, L. Rozenstein-Tsalkovich, J. Turnbull, V. Weiner, L. Chama, I. Lerer, S. Shpitzen, E. Leitersdorf, C. Paradas, M. Wallace, R. Schiffmann, S. DiMauro, A. Lossos, B.A. Minassian, Deep intronic GBE1 mutation in manifesting heterozygous patients with adult polyglucosan body disease, *JAMA Neurol.* 72 (2015) 441–445.

- [76] O.H. Akman, O. Kakhlon, J. Coku, L. Peverelli, H. Rosenmann, L. Rozenstein-Tsalkovich, J. Turnbull, V. Meiner, L. Chama, I. Lerer, S. Shpitzen, E. Leitersdorf, C.P. Lopez, M. Wallace, R. Schiffmann, S. Di Mauro, A. Lossos, B. Minassian, An exon trap with proper polyA site in the GBE1 is the common missing cause in adult polyglucosan body disease, *Neurology* 84 (2015).
- [77] C. Bruno, S. Servidei, S. Shanske, G. Karpati, S. Carpenter, D. McKee, R.J. Barohn, M. Hirano, Z. Rifai, S. DiMauro, Glycogen branching enzyme deficiency in adult polyglucosan body disease, *Ann. Neurol.* 33 (1993) 88–93.
- [78] E. Szymańska, S. Szymańska, G. Truszkowska, E. Ciara, M. Pronicki, Y.S. Shin, T. Podskarbi, A. Kępka, M. Śpiewak, R. Płoski, Z.T. Bilińska, D. Rokicki, Variable clinical presentation of glycogen storage disease type IV: from severe hepatosplenomegaly to cardiac insufficiency. Some discrepancies in genetic and biochemical abnormalities, *Arch. Med. Sci.* 14 (2018) 237–247.
- [79] E. Sindern, F. Ziemssen, T. Ziemssen, T. Podskarbi, Y. Shin, F. Brasch, K.M. Müller, J.M. Schroder, J.P. Malin, M. Vorgerd, Adult polyglucosan body disease: a postmortem correlation study, *Neurology* 61 (2003) 263–265.
- [80] E. Lausberg, S. Gießelmann, J.P. Dewulf, E. Wiame, A. Holz, R. Salvarinova, C.D. van Karnebeek, P. Klemm, K. Ohl, M. Mull, T. Braunschweig, J. Weis, C.J. Sommer, S. Demuth, C. Haase, C. Stollbrink-Peschgens, F.G. Debray, C. Libioule, D. Choukair, P.T. Oommen, A. Borkhardt, H. Surowy, D. Wiczorek, N. Wagner, R. Meyer, T. Eggermann, M. Begemann, E. Van Schaftingen, M. Häusler, K. Tenbrock, L. van den Heuvel, M. Elbracht, I. Kurth, F. Kraft, C2orf69 mutations disrupt mitochondrial function and cause a multisystem human disorder with recurring autoinflammation, *J. Clin. Invest.* 131 (2021).
- [81] H.L. Greene, F.K. Ghishan, B. Brown, D.T. McClenathan, D. Freese, Hypoglycemia in type IV glycogenosis: hepatic improvement in two patients with nutritional management, *J. Pediatr.* 112 (1988) 55–58.
- [82] P.D. Maaswinkel-Mooy, B.J.H.M. Poorthuis, H.H. Van Gelderen, J.J.P. Van De Kamp, Dicarboxylic aciduria and secondary carnitine deficiency in glycogenosis type IV, *Arch. Dis. Child.* 62 (1987) 1066–1067.
- [83] P.M. Cox, L.A. Brueton, K.W. Murphy, V.C. Worthington, P. Bjelogric, E.J. Lazda, N.J. Sabire, C.A. Sewry, Early-onset fetal hydrops and muscle degeneration in siblings due to a novel variant of type IV glycogenosis, *Am. J. Med. Genet.* 86 (1999) 187–193.
- [84] A. L'Herminé-Coulomb, F. Beuzen, R. Bouvier, M.O. Rolland, R. Froissart, F. Menez, F. Audibert, P. Labrune, Fetal type IV glycogen storage disease: clinical, enzymatic, and genetic data of a pure muscular form with variable and early antenatal manifestations in the same family, *Am. J. Med. Genet. A* 139 A (2005) 118–122.
- [85] I. Colombo, S. Pagliarini, S. Testolin, E. Salsano, L.M. Napoli, A. Bordon, S. Salani, E. D'Adda, L. Morandi, L. Farina, F. Magri, M. Riva, A. Prella, M. Sciacco, G.P. Comi, M. Moggi, Adult polyglucosan body disease: clinical and histological heterogeneity of an Italian family, *Neuromuscul. Disord.* 25 (2015) 423–428.
- [86] M.A. Chen, D.A. Weinstein, Glycogen storage diseases: diagnosis, treatment and outcome, *Transl. Sci. Rare Dis.* 1 (2016) 45–72.
- [87] J. Hicks, E. Wartchow, G. Mierau, Glycogen storage diseases: a brief review and update on clinical features, genetic abnormalities, pathologic features, and treatment, *Ultrastruct. Pathol.* 35 (2011) 183–196.
- [88] P.L. Magoulas, A.W. El-Hattab, A. Roy, D.S. Bali, M.J. Finegold, W.J. Craig, Diffuse reticuloendothelial system involvement in type IV glycogen storage disease with a novel GBE1 mutation: a case report and review, *Hum. Pathol.* 43 (2012) 943–951.
- [89] S. Sreekantam, H. Rizvi, R. Brown, S. Santra, J. Raiman, S. Vijay, P.J. McKiernan, G.L. Gupta, An uncommon cause of early infantile liver disease and raised chitotriosidase, *J. Inherited Metab. Dis.* 43 (2020) 22–24.
- [90] G.A. Bannayan, W.J. Dean, R.R. Howell, Type IV glycogen storage disease. Light microscopic, electron microscopic, and enzymatic study, *Am. J. Clin. Pathol.* 66 (1976) 702–709.
- [91] L. Dainese, M.L. Monin, S. Demeret, G. Brochier, R. Froissart, A. Spraul, R. Schiffmann, D. Seilhean, F. Mochel, Abnormal glycogen in astrocytes is sufficient to cause adult polyglucosan body disease, *Gene* 515 (2013) 376–379.
- [92] E. Krim, A. Vital, F. Macia, F. Yekhelef, F. Tison, Atypical parkinsonism combining alpha-synuclein inclusions and polyglucosan body disease, *Mov. Disord.* 20 (2005) 200–204.
- [93] M. Berkhoff, J. Weis, G. Schroth, M. Sturzenegger, Extensive white-matter changes in case of adult polyglucosan body disease, *Neuroradiology* 43 (2001) 234–236.
- [94] T. Wierzbza-Bobrowicz, E. Lewandowska, T. Stepień, J. Modzelewska, Immunohistochemical and ultrastructural changes in the brain in probable adult glycogenosis type IV: adult polyglucosan body disease, *Folia Neuropathol.* 46 (2008) 165–175.
- [95] T.D. McDonald, P.L. Faust, C. Bruno, S. DiMauro, J.E. Goldman, Polyglucosan body disease simulating amyotrophic lateral sclerosis, *Neurology* 43 (1993) 785–790.
- [96] C.H. Hajdu, J.H. Lefkowitz, Adult polyglucosan body disease: a rare presentation with chronic liver disease and ground-glass hepatocellular inclusions, *Semin. Liver Dis.* 31 (2011) 223–229.
- [97] J.I. Wolfsdorf, I.A. Holm, D.A. Weinstein, Glycogen storage disease. Phenotypic, genetic, and biochemical characteristics, and therapy, *Endocrinol. Metab. Clin. N. Am.* 28 (1999) 801–823.
- [98] M. Ersoy, Z. Onal, A novel mutation of the GBE1 gene in a patient with the non-progressive hepatic form of type IV glycogen storage disease, *J. Inherited Metab. Dis.* 38 (2015) S183.
- [99] S. Assereto, O.P. van Diggelen, L. Diogo, E. Morava, D. Cassandrini, I. Carreira, W.P. de Boode, J. Dilling, P. Garcia, M. Henriques, O. Rebelo, H. ter Laak, C. Minetti, C. Bruno, Null mutations and lethal congenital form of glycogen storage disease type IV, *Biochem. Biophys. Res. Commun.* 361 (2007) 445–450.
- [100] S.K.H. Tay, H.O. Akman, W.K. Chung, M.G. Pike, F. Muntoni, A.P. Hays, S. Shanske, S.J. Valberg, J.R. Mickelson, K. Tanji, S. DiMauro, Fatal infantile neuromuscular presentation of glycogen storage disease type IV, *Neuromuscul. Disord.* 14 (2004) 253–260.
- [101] S.W. Biggins, P. Angeli, G. Garcia-Tsao, P. Ginès, S.C. Ling, M.K. Nadim, F. Wong, W.R. Kim, Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases Hepatology (Baltimore, Md.), vol. 74, 2021 1014–1048.
- [102] G. Garcia-Tsao, J.G. Abraldes, A. Berzigotti, J. Bosch, Portal Hypertensive Bleeding in Cirrhosis: Risk Stratification, Diagnosis, and Management: 2016 Practice Guidance by the American Association for the Study of Liver Diseases Hepatology (Baltimore, Md.), vol. 65, 2017 310–335.
- [103] N.S. Alshak, J. Cocjin, L. Podesta, R. van de Velde, L. Makowka, P. Rosenthal, S.A. Geller, Hepatocellular adenoma in glycogen storage disease type IV, *Arch. Pathol. Lab. Med.* 118 (1994) 88–91.
- [104] E. Demo, D. Frush, M. Gottfried, J. Koepke, A. Boney, D. Bali, Y.T. Chen, P.S. Kishnani, Glycogen storage disease type III-hepatocellular carcinoma a long-term complication? *J. Hepatol.* 46 (2007) 492–498.
- [105] L.M. Franco, V. Krishnamurthy, D. Bali, D.A. Weinstein, P. Arn, B. Clary, A. Boney, J. Sullivan, D.P. Frush, Y.T. Chen, P.S. Kishnani, Hepatocellular carcinoma in glycogen storage disease type Ia: a case series, *J. Inherited Metab. Dis.* 28 (2005) 153–162.
- [106] P.S. Kishnani, S.L. Austin, P. Arn, D.S. Bali, A. Boney, L.E. Case, W.K. Chung, D.M. Desai, A. El-Gharbawy, R. Haller, G. Peter, A. Smit, A.D. Smith, L.D.A. Hobson-Webb, Glycogen Storage Disease Type III diagnosis and management guidelines, *Genet. Med.* 12 (2010).
- [107] P.S. Kishnani, S.L. Austin, J.E. Abdenur, P. Arn, D.S. Bali, A. Boney, W.K. Chung, A.I. Dagli, D. Dale, D. Koeberl, M.J. Somers, S.B. Wechsler, D.A. Weinstein, J.I. Wolfsdorf, M.S. Watson, Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics, *Genet. Med.* 16 (2014) e1.
- [108] M.K. Ndugga-Kabuye, J. Maleszewski, S. Chanprasert, K.D. Smith, Glycogen storage disease type IV: Dilated cardiomyopathy as the isolated initial presentation in an adult patient, *BMJ Case Rep.* 12 (2019).
- [109] V. Hemsrichart, S. Karalak, K. Thakerngpol, T. Stitnimakarn, Type IV glycogen storage disease: first reported case in Thailand, *J. Med. Assoc. Thai.* 72 (1989) 697–700.
- [110] V.J. Ferrans, R.G. Hibbs, J.J. Walsh, G.E. Burch, Cardiomyopathy, cirrhosis of the liver and deposits of a fibrillar polysaccharide. Report of a case with histochemical and electron microscopic studies, *Am. J. Cardiol.* 17 (1966) 457–469.
- [111] T. Aksu, A. Colak, O. Tufekcioglu, Cardiac involvement in glycogen storage disease type IV: two cases and the two ends of a spectrum case, *Rep. Med.* 2012 (2012) 764286.
- [112] E. Sindern, F. Ziemssen, T. Ziemssen, T. Podskarbi, Y. Shin, F. Brasch, K.M. Müller, J.M. Schroder, J.P. Malin, M. Vorgerd, Adult polyglucosan body disease: a postmortem correlation study, *Neurology* 61 (2003) 263–265.
- [113] S. Nase, K.P. Kunze, M. Sigmund, J.M. Schroeder, Y. Shin, P. Hanrath, A new variant of type IV glycogenosis with primary cardiac manifestation and complete branching enzyme deficiency. In vivo detection by heart muscle biopsy, *Eur. Heart J.* 16 (1995) 1698–1704.
- [114] R. Ewert, A. Gulijew, R. Wensel, M. Dandel, M. Hummel, M. Vogel, R. Meyer, R. Hetzer, Glycogenosis type IV as a seldom cause of cardiomyopathy - report about a successful heart transplantation, *Z. Kardiol.* 88 (1999) 850–856.
- [115] M.K. Ndugga-Kabuye, J. Maleszewski, S. Chanprasert, K.D. Smith, Glycogen storage disease type IV: dilated cardiomyopathy as the isolated initial presentation in an adult patient, *BMJ Case Rep.* 12 (2019).
- [116] S. Lyo, J. Miles, J. Meisner, M. Guelfgaut, Case report: adult-onset manifesting heterozygous glycogen storage disease type IV with dilated cardiomyopathy and absent late gadolinium enhancement on cardiac magnetic resonance imaging, *Eur. Heart J. - Case Rep.* 4 (2020) 1–6.
- [117] P.F. Kantor, J. Loughheed, A. Dancas, M. McGillion, N. Barbosa, C. Chan, R. Dillenburg, J. Atallah, H. Buchholz, C. Chant-Gambacort, J. Conway, L. Gardin, K. George, S. Greenway, D.G. Human, A. Jeewa, J.F. Price, R.D. Ross, S.L. Roche, L. Ryerson, R. Soni, J. Wilson, K. Wong, Presentation, diagnosis, and medical management of heart failure in children: Canadian cardiovascular society guidelines, *Can. J. Cardiol.* 29 (2013) 1535–1552.
- [118] S.E. Lipshultz, Y.M. Law, A. Asante-Korang, E.D. Austin, A.I. Dipchand, M.D. Everitt, D.T. Hsu, K.Y. Lin, J.F. Price, J.D. Wilkinson, S.D. Colan, Cardiomyopathy in children: classification and diagnosis: a scientific statement from the American Heart Association, *Circulation* 140 (2019) e9–e68.
- [119] S.R. Ommen, S. Mital, M.A. Burke, S.M. Day, A. Deswal, P. Elliott, L.L. Evanovich, J. Hung, J.A. Joglar, P. Kantor, C. Kimmelstiel, M. Kittleson, M.S. Link, M.S. Maron, M.W. Martinez, C.Y. Miyake, H.V. Schaff, C. Semsarian, P. Sorajja, AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines, *Circulation* 142 (2020) e558–e631.
- [120] C.W. Yancy, M. Jessup, B. Bozkurt, J. Butler, D.E. Casey, M.M. Colvin, M.H. Drazner, G.S. Filippatos, G.C. Fonarow, M.M. Givertz, S.M. Hollenberg, J. Lindenfeld, F.A. Masoudi, P.E. McBride, P.N. Peterson, L.W. Stevenson, C. Westlake, ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America, *Circulation* 136 (2017) e137–e161.
- [121] R.H. Squires, V. Ng, R. Romero, U. Ekong, W. Hardikar, S. Emre, G.V. Mazariegos, Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology,

- Hepatology and Nutrition Hepatology (Baltimore, Md.), vol. 60, 2014, pp. 362–398.
- [122] P.S. Kishnani, J. Goldstein, S.L. Austin, P. Arn, B. Bachrach, D.S. Bali, W.K. Chung, A. El-Gharbawy, L.M. Brown, S. Kahler, S. Pendyal, K.M. Ross, L. Tsilianidis, D.A. Weinstein, M.S. Watson, Diagnosis and management of glycogen storage diseases type VI and IX: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG), *Genet. Med.* 21 (2019) 772–789.
 - [123] M.K. Davis, D.A. Weinstein, Liver transplantation in children with glycogen storage disease: controversies and evaluation of the risk/benefit of this procedure, *Pediatr. Transplant.* 12 (2008) 137–145.
 - [124] R. Selby, T.E. Starzl, E. Yunis, S. Todo, A.G. Tzakis, B.I. Brown, R.S. Kendall, Liver transplantation for type I and type IV glycogen storage disease, *Eur. J. Pediatr.* 152 (1993) S71–S76.
 - [125] T.E. Starzl, A.J. Demetris, M. Trucco, C. Ricordi, S. Ildstad, P.I. Terasaki, N. Murase, R.S. Kendall, M. Kocova, W.A. Rudert, A. Zeevi, D. Van Thiel, Chimerism after liver transplantation for type IV glycogen storage disease and type 1 Gaucher's disease, *N. Engl. J. Med.* (1993) 745–749.
 - [126] Z. Beyzaei, A. Shamsaeifar, K. Kazemi, S. Nikeghbalian, A. Bahador, M. Dehghani, S.-A. Malekhosseini, B. Geramizadeh, Liver transplantation in glycogen storage disease: a single-center experience, *Orphanet J. Rare Dis.* 17 (2022) 127.
 - [127] E.B. Bostanci, V. Öter, I. Özer, N. Turhan, M. Aközü, Living donor liver transplantation for glycogen storage disease type IV; a case report, *Hepatol. Int.* 9 (2015) S353.
 - [128] P. Rosenthal, L. Podesta, R. Grier, J.W. Said, L. Sher, J. Cocjin, F. Watanabe, E. Vasiliauskas, R. van de Velde, L. Makowka, Failure of liver transplantation to diminish cardiac deposits of amylopectin and leukocyte inclusions in type IV glycogen storage disease, *Liver Transplant. Surg.* 1 (1995) 373–376.
 - [129] S. Willot, V. Marchand, A. Rasquin, F. Alvarez, S.R. Martin, Systemic progression of type IV glycogen storage disease after liver transplantation, *J. Pediatr. Gastroenterol. Nutr.* 51 (2010) 661–664.
 - [130] A.B. Cochran, S.E. Fedson, D.C. Cronin II, Nesiritide as bridge to multi-organ transplantation: a case report, *Transplant. Proc.* 39 (2007) 308–310.
 - [131] H. Zellweger, S. Mueller, V. Ionasescu, S.S. Schochet, W.F. McCormick, Glycogenosis IV: a new cause of infantile hypotonia, *J. Pediatr.* 80 (1972) 839–842.
 - [132] Y. Bao, P. Kishnani, J.Y. Wu, Y.T. Chen, Hepatic and neuromuscular forms of glycogen storage disease type IV caused by mutations in the same glycogen-branching enzyme gene, *J. Clin. Invest.* 97 (1996) 941–948.
 - [133] T.A. Burrow, R.J. Hopkin, K.E. Bove, L. Miles, B.L. Wong, A. Choudhary, D. Bali, S.C. Li, Y.T. Chen, Non-lethal congenital hypotonia due to glycogen storage disease type IV, *Am. J. Med. Genet.* 140 A (2006) 878–882.
 - [134] E. Malfatti, C. Barnerias, C. Hedberg-Oldfors, C. Gitiaux, A. Benezit, A. Oldfors, R.Y. Carlier, S. Quijano-Roy, N.B. Romero, A Novel Neuromuscular Form of Glycogen Storage Disease Type IV with Arthrogryposis, Spinal Stiffness and Rare Polyglucosan Bodies in Muscle, *Neuromuscular Disorders*, Elsevier Ltd, 2016 681–687.
 - [135] T. Sandhu, M. Polan, Z. Yu, R. Lu, A. Makkar, Case of neonatal fatality from neuromuscular variant of glycogen storage disease type IV, *J. Inherited Metab. Dis. Rep.* (2019) 51–55.
 - [136] M.C. Walter, S. Wenninger, A. Abicht, Glycogen storage disease type iv presenting as congenital myopathy with contractures and rigid spine, *J. Neuromusc. Dis.* 5 (2018) S204–S205.
 - [137] P.V.S. Souza, B.M.L. Badia, I.B. Farias, W.B.V.D.R. Pinto, A.S.B. Oliveira, H.O. Akman, S. DiMauro, GBE1-related disorders: adult polyglucosan body disease and its neuromuscular phenotypes, *J. Inherit. Metab. Dis.* 44 (2021) 534–543.
 - [138] P.T. Zebhauser, I. Cordts, H. Hengel, B. Haslinger, P. Lingor, H.O. Akman, T.B. Haack, M. Deschauer, Characterization of cognitive impairment in adult polyglucosan body disease, *J. Neurol.* 269 (2022) 2854–2861.
 - [139] S. Billot, D. Hervé, H.O. Akman, R. Froissart, C. Baussan, K.G. Claeys, M. Piraud, F. Sedel, F. Mochel, P. Laforêt, Acute but transient neurological deterioration revealing adult polyglucosan body disease, *J. Neurol. Sci.* 324 (2013) 179–182.
 - [140] P.V.S. Souza, T. Bortholin, R.B. Dias, M.A.T. Chieia, S. Burlin, F.G.M. Naylor, W. Pinto, A.S.B. Oliveira, New genetic causes for complex hereditary spastic paraplegia, *J. Neurol. Sci.* 379 (2017) 283–292.
 - [141] K. Segers, H. Kadhim, C. Colson, R. Duttman, G. Glibert, Adult polyglucosan body disease masquerading as “ALS with dementia of the Alzheimer type”: an exceptional phenotype in a rare pathology, *Alzheimer Dis. Assoc. Disord.* 26 (2012) 96–99.
 - [142] N.P. Robertson, S. Wharton, J. Anderson, N.J. Scolding, Adult polyglucosan body disease associated with an extrapyramidal syndrome, *J. Neurol. Neurosurg. Psychiatry* 65 (1998) 788–790.
 - [143] J.R. Trivedi, G.I. Wolfe, S.P. Nations, D.K. Burns, W.W. Bryan, R.B. Dewey, Adult polyglucosan body disease associated with Lewy bodies and tremor, *Arch. Neurol.* 60 (2003) 764–766.
 - [144] E.H. Bigio, M.F. Weiner, F.J. Bonte, C.L. White, Familial dementia due to adult polyglucosan body disease, *Clin. Neuropathol.* 16 (1997) 227–234.
 - [145] E.N. Bit-Ivan, K.-H. Lee, D. Gitelman, S. Weintraub, M. Mesulam, R. Rademakers, A.M. Isaacs, K.J. Hatanpaa, C.L.R. White, Q. Mao, O. Akman, S. DiMauro, E.H. Bigio, Adult polyglucosan body disease with GBE1 haploinsufficiency and concomitant frontotemporal lobar degeneration, *Neuropathol. Appl. Neurobiol.* 40 (2014) 778–782.
 - [146] P. Boulan-Predseil, A. Vital, B. Brochet, D. Darriet, P. Henry, C. Vital, Dementia of frontal lobe type due to adult polyglucosan body disease, *J. Neurol.* 242 (1995) 512–516.
 - [147] J.G. Farmer, B.J. Crain, B.T. Harris, R.S. Turner, Coexisting adult polyglucosan body disease with frontotemporal lobar degeneration with transactivation response DNA-binding protein-43 (TDP-43)-positive neuronal inclusions, *Neurocase* 19 (2013) 67–75.
 - [148] E. Naddaf, C.D. Kassardjian, Y.G. Kurt, H.O. Akman, A.J. Windebank, Adult polyglucosan body disease presenting as a unilateral progressive plexopathy, *Muscle Nerve* 53 (2016) 976–981.
 - [149] Y. Harigaya, T. Matsukawa, Y. Fujita, K. Mizushima, H. Ishiura, J. Mitsui, S. Morishita, M. Shoji, Y. Ikeda, S. Tsuji, Novel GBE1 mutation in a Japanese family with adult polyglucosan body disease, *Genetics* 3 (2017) e138–e138.
 - [150] M. Nicholas, V. Haute, G. Carino, An unexpected case of adult polyglucosan body disease, *Crit. Care Med.* 38 (2010) A278.
 - [151] B.J. Balin, C.J. Hammond, K.E. Galluzzi, Intriguing mixed pathologic features in a Case of dementia with Lewy bodies the, *J. Am. Osteopath. Assoc.* 119 (2019) 632–636.
 - [152] C. Grunseich, N. Sarkar, J. Lu, M. Owen, A. Schindler, P.A. Calabresi, C.J. Sumner, R.H. Roda, V. Chaudhury, T.E. Lloyd, T.O. Crawford, S.H. Subramony, S.J. Oh, P. Richardson, K. Tanji, J.Y. Kwan, K.H. Fischbeck, A. Mankodi, Improving the efficacy of exome sequencing at a quaternary care referral centre: novel mutations, clinical presentations and diagnostic challenges in rare neurogenetic diseases, *J. Neurol. Neurosurg. Psychiatry* 92 (2021) 1186–1196.
 - [153] F. Gray, R. Gherardi, A. Marshall, I. Janota, J. Poirier, Adult polyglucosan body disease (APBD), *J. Neuropathol. Exp. Neurol.* 47 (1988) 459–474.
 - [154] D. Bathgate, R. Wigley, G. Gorman, R. Horvath, P.F. Chinnery, Childhood presentation of “adult” polyglucosan body disease: Normal GBE1 sequence with no glycogen branching enzyme activity, *Ann. Neurol.* 73 (2013) 317–318.
 - [155] R. Massa, C. Bruno, A. Martorana, N. de Stefano, O.P. van Diggelen, A. Federico, Adult polyglucosan body disease: proton magnetic resonance spectroscopy of the brain and novel mutation in the GBE1 gene, *Muscle Nerve* 37 (2008) 530–536.
 - [156] D.A. Ginsberg, T.B. Boone, A.P. Cameron, A. Gousse, M.R. Kaufman, E. Keays, M.J. Kennelly, G.E. Lemack, E.S. Rovner, L.H. Souter, C.C. Yang, S.R. Kraus, The AUA/SUFU guideline on adult neurogenic lower urinary tract dysfunction: diagnosis and evaluation, *J. Urol.* 206 (2021) 1097–1105.
 - [157] D.J. Lightner, A. Gomelsky, L. Souter, S.P. Vasavada, Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment 2019, *J. Urol.* 202 (2019) 558–563.
 - [158] H.K. Katsumi, J.F. Kalisvaart, L.D. Ronningen, R.M. Hovey, Urethral versus suprapubic catheter: choosing the best bladder management for male spinal cord injury patients with indwelling catheters, *Spinal Cord* 48 (2010) 325–329.
 - [159] G. Menculini, E. Chipi, F. Paolini Paoletti, L. Gaetani, P. Nigro, S. Simoni, A. Mancini, N. Tambasco, M. Di Filippo, A. Tortorella, L. Parnetti, Insights into the pathophysiology of psychiatric symptoms in central nervous system disorders: implications for early and differential diagnosis, *Int. J. Mol. Sci.* 22 (2021).
 - [160] M. Husain, Transdiagnostic neurology: neuropsychiatric symptoms in neurodegenerative diseases, *Brain* 140 (2017) 1535–1536.
 - [161] C. Silveira, R. Guedes, D. Maia, R. Curral, R. Coelho, Neuropsychiatric Symptoms of Multiple Sclerosis: State of the Art, *Psychiatry Investig.* 16 (2019) 877–888.
 - [162] P. Vinci, P. Gargiulo, M. Panunzi, L. Baldini, Psychological distress in patients with Charcot-Marie-Tooth disease, *Eur. J. Phys. Rehab. Med.* 45 (2009) 385–389.
 - [163] C.R. Roe, F. Mochel, Anaplerotic diet therapy in inherited metabolic disease: therapeutic potential, *J. Inherit. Metab. Dis.* 29 (2006) 332–340.
 - [164] C.R. Roe, T. Bottiglieri, M. Wallace, E. Arning, A. Martin, Adult Polyglucosan body disease (APBD): Anaplerotic diet therapy (Triheptanoin) and demonstration of defective methylation pathways, *Mol. Genet. Metab.* 101 (2010) 246–252.
 - [165] R. De Amicis, A. Leone, S. Ravasenghi, G. Scigliuolo, E. Mauro, E. Salsano, A. Battezzati, S. Bertoli, Triheptanoin supplementation does not affect nutritional status: a Case report of two siblings with adult polyglucosan body disease, *J. Am. Coll. Nutr.* 39 (2020) 557–562.
 - [166] T. Goldberg, A.E. Slonim, Nutrition therapy for hepatic glycogen storage diseases, *J. Am. Diet. Assoc.* (1993) 1423–1430.
 - [167] J.Y. Meek, L. Noble, B. Section on, policy statement: breastfeeding and the use of Human Milk, *Pediatrics* 150 (2022) e2022057988.
 - [168] R.D. Stevenson, Use of segmental measures to estimate stature in children with cerebral palsy, *Arch. Pediatr. Adolesc. Med.* 149 (1995) 658–662.
 - [169] A. Carvalho, J. Nunes, R. Taipa, M. Melo Pires, J. Pinto Basto, P. Barros, Adult polyglucosan body disease—an atypical compound heterozygous with a novel GBE1 mutation, *Neurol. Sci.* 42 (2021) 2955–2959.
 - [170] V. Ramaglia, O. Rojas, I. Naouar, J.L. Gommerman, The ins and outs of central nervous system inflammation—lessons learned from multiple sclerosis, *Annu. Rev. Immunol.* 39 (2021) 199–226.
 - [171] J. Hirrlinger, K.A. Nave, Adapting brain metabolism to myelination and long-range signal transduction, *Glia* 62 (2014) 1749–1761.
 - [172] S. Pan, J.R. Chan, Regulation and dysregulation of axon infrastructure by myelinating glia, *J. Cell Biol.* 216 (2017) 3903–3916.
 - [173] C. Escartin, E. Galea, A. Lakatos, J.P. O’Callaghan, G.C. Petzold, A. Serrano-Pozo, C. Steinhäuser, A. Volterra, G. Carmignoto, A. Agarwal, N.J. Allen, A. Araque, L. Barbeito, A. Barzilai, D.E. Bergles, G. Bonvento, A.M. Butt, W.T. Chen, M. Cohen-Salmon, C. Cunningham, B. Deneen, B. De Strooper, B. Díaz-Castro, C. Farina, M. Freeman, V. Gallo, J.E. Goldman, S.A. Goldman, M. Götz, A. Gutiérrez, P.G. Hayden, D.H. Heiland, E.M. Hol, M.G. Holt, M. Iino, K.V. Kastanenka, H. Kettenmann, B.S. Khakh, S. Koizumi, C.J. Lee, S.A. Liddelow, B.A. MacVicar, P. Magistretti, A. Messing, A. Mishra, A.V. Molofsky, K.K. Murai, C.M. Norris, S. Okada, S.H.R. Olliet, J.F. Oliveira, A. Panatier, V. Parpura, M. Pekna, M. Pekny, L. Pellerin, G. Perea, B.G. Pérez-Nievas, F.W. Pfrieger, K.E. Poskanzer, F.J. Quintana, R.M. Ransohoff, M. Riquelme-Perez, S. Robel, C.R. Rose, J.D. Rothstein, N. Rouach, D.H. Rowitch, A. Semyanov, S. Sirko, H. Sontheimer, R.A. Swanson, J. Vitorica, I.B. Wanner, L.B. Wood, J. Wu, B. Zheng, E.R. Zimmer, R. Zorec, M.V. Sofroniew, A. Verkhratsky, Reactive astrocyte nomenclature, definitions, and future directions, *Nat. Neurosci.* 24 (2021) 312–325.

- [176] N.J. Allen, D.A. Lyons, *Glia as Architects of Central Nervous System Formation and Function Science* (New York, N.Y.), vol. 362, 2018 181–185.
- [177] B.L. Guerrero, N.L. Sicotte, Microglia in multiple sclerosis: friend or foe? *Front. Immunol.* 11 (2020) 374.
- [178] E. Gumusgoz, S. Kasiri, D.R. Guisso, J. Wu, M. Dear, B. Verhalen, B.A. Minassian, AAV-mediated artificial miRNA reduces pathogenic polyglucosan bodies and neuroinflammation in adult polyglucosan body and lafora disease mouse models, *Neurotherapeutics* 19 (2022) 982–993.
- [179] H. Yi, F. Gao, S. Austin, P.S. Kishnani, B. Sun, Alglucosidase Alfa Treatment Alleviates Liver Disease in a Mouse Model of Glycogen Storage Disease Type IV, *Molecular Genetics and Metabolism Reports*, Elsevier Inc., 2016 31–33.
- [180] H. Yi, Q. Zhang, E.D. Brooks, C. Yang, B.L. Thurberg, P.S. Kishnani, B. Sun, Systemic correction of murine glycogen storage disease type IV by an AAV-mediated gene therapy, *Hum. Gene Ther.* 28 (2017) 286–294.
- [181] O. Kakhlon, I. Ferreira, L.J. Solmesky, N. Khazanov, A. Lossos, R. Alvarez, D. Yetil, S. Pampou, M. Weil, H. Senderowitz, P. Escriba, W.W. Yue, H.O. Akman, Guaiacol as a drug candidate for treating adult polyglucosan body disease, *JCI Insight* 3 (2018).
- [182] O. Kakhlon, H. Vaknin, K. Mishra, J. D'Souza, M. Marisat, U. Sprecher, S. Wald-Altmann, A. Dukhovny, Y. Raviv, B. Da'adoosh, H. Engel, S. Benhamron, K. Nitzan, S. Sweetat, A. Permyakova, A. Mordechai, H.O. Akman, H. Rosenmann, A. Lossos, J. Tam, B.A. Minassian, M. Weil, Alleviation of a polyglucosan storage disorder by enhancement of autophagic glycogen catabolism, *EMBO Mol. Med.* 13 (2021), e14554.
- [183] H. Hizarcioglu-Gulsen, A. Yuce, Z. Akcoren, B. Berberoglu-Ates, Y. Aydemir, E. Sag, S. Ceylaner, A rare cause of elevated chitotriosidase activity: Glycogen storage disease type IV, *J. Inherited Metab. Dis. Rep.* 17 (2014) 63–66.
- [184] H. Michelakakis, E. Dimitriou, I. Labadaridis, The expanding spectrum of disorders with elevated plasma chitotriosidase activity: an update, *J. Inherit. Metab. Dis.* 27 (2004) 705–706.
- [185] J. Kumlien, M.A. Chester, B.S. Lindberg, P. Pizzo, D. Zopf, A. Lundblad, Urinary excretion of a glucose-containing tetrasaccharide: a parameter for increased degradation of glycogen, *Clin. Chim. Acta* 176 (1988) 39–48.
- [186] S.P. Young, M. Piraud, J.L. Goldstein, H. Zhang, C. Rehder, P. Laforet, P.S. Kishnani, D.S. Millington, M.R. Bashir, D.S. Bali, Assessing disease severity in Pompe disease: the roles of a urinary glucose tetrasaccharide biomarker and imaging techniques *American journal of medical genetics part C: seminars in medical, Genetics* 160c (2012) 50–58.
- [187] C.A. Halaby, S.P. Young, S. Austin, E. Stefanescu, D. Bali, L.K. Clinton, B. Smith, S. Pendyal, J. Upadia, G.R. Schooler, A.M. Mavis, P.S. Kishnani, Liver fibrosis during clinical ascertainment of glycogen storage disease type III: a need for improved and systematic monitoring, *Genet. Med.* 21 (2019) 2686–2694.
- [188] M.R. Heiner-Fokkema, J. van der Krogt, F. de Boer, M.J. Fokkert-Wilts, R.G.H.J. Maatman, I.J. Hoogeveen, T.G.J. Derks, The multiple faces of urinary glucose tetrasaccharide as biomarker for patients with hepatic glycogen storage diseases, *Genet. Med.* 22 (2020) 1915–1916.
- [189] W. Sluiter, J.C. Van Den Bosch, D.A. Goudriaan, C.M. Van Gelder, J.M. De Vries, J.G.M. Huijtmans, A.J.J. Reuser, A.T. Van Der Ploeg, G.J.G. Ruijter, Rapid ultraperformance liquid chromatography-tandem mass spectrometry assay for a characteristic glycogen-derived tetrasaccharide in pompe disease and other glycogen storage diseases, *Clin. Chem.* 58 (2012) 1139–1147.
- [190] M.S. Cafferty, R.E. Lovelace, A.P. Hays, S. Serveidei, S. Dimauro, L.P. Rowland, Polyglucosan body disease, *Muscle Nerve* 14 (1991) 102–107.
- [191] A.J.M. Vos, E.M.G. Joosten, A.A.W.M. Gabreëls-Festen, Adult polyglucosan body disease: Clinical and nerve biopsy findings in two cases, *Annals of Neurology* 13 (1983) 440–444.
- [192] S. Inoue, R. Ishii, H. Fukuda, K. Saitoh, R. Shimizu, Sevoflurane anaesthesia for a patient with adult polyglucosan body disease, *Canadian Journal of Anaesthesia* 43 (1996) 1257–1259.
- [193] E. Gumusgoz, D.R. Guisso, S. Kasiri, J. Wu, M. Dear, B. Verhalen, S. Nitschke, S. Mitra, F. Nitschke, B.A. Minassian, Targeting gys1 with AAV-SaCas9 decreases pathogenic polyglucosan bodies and neuroinflammation in adult polyglucosan body and lafora disease mouse models, *Neurotherapeutics* 18 (2021) 1414–1425.