Glycogen branching enzyme deficiency (glycogen storage disease IV,
 Andersen disease, APBD)

Monday, December 19, 2016, 7:13 AM
                ©2016
 UpToDate
                ®

        Official Topic from UpToDate®,
        the clinical decision support resource accessed by 700,000+
 clinicians worldwide. Available via the web and mobile
 devices,
        subscribe to UpToDate® at [www.uptodate.com/store](http://www.uptodate.com/store).

 Glycogen
 branching enzyme deficiency (glycogen storage disease IV,
 Andersen disease)Authors
 William J Craigen, MD, PhD
 Basil T Darras, MD
 Section
 Editor
 Sihoun Hahn, MD, PhD
 Deputy
 Editor
 Elizabeth TePas, MD, MS
 All
 topics are updated as new evidence becomes available and our
 peer review process is complete.Literature
 review current through: Nov
 2016. | This
 topic last updated: May 08, 2015.INTRODUCTION — Glycogen
 is the stored form of glucose and serves as a buffer for
 glucose needs. It is composed of long polymers of a 1-4
 linked glucose, interrupted by a 1-6 linked branch point
 every 4 to 10 residues. Glycogen is formed in periods of
 dietary carbohydrate loading and broken down when glucose
 demand is high or dietary availability is low (figure
 1).There are a number of inborn errors of glycogen
 metabolism that result from mutations in genes for virtually
 all of the proteins involved in glycogen synthesis,
 degradation, or regulation. Those disorders that result in
 abnormal storage of glycogen are known as glycogen storage
 diseases (GSDs). They have largely been categorized by
 number, according to the chronology of recognition of the
 responsible enzyme defect (table 1). The age of onset varies
 from in utero to adulthood.Glycogen is most abundant
 in liver and muscle, which are most affected by these
 disorders. The physiologic importance of a given enzyme in
 liver and muscle determines the clinical manifestations of
 the disease.●The
 main role of glycogen in the liver is to store glucose for
 release to tissues that are unable to synthesize significant
 amounts during fasting. The major manifestations of
 disorders of glycogen metabolism affecting the liver are
 hypoglycemia and hepatomegaly. (See "Physiologic
 response to hypoglycemia in normal subjects and patients
 with diabetes mellitus".)●Glycogen
 is the primary source of energy for high-intensity muscle
 activity by providing substrates for the generation of
 adenosine triphosphate (ATP). The major manifestations of
 disorders of glycogen metabolism affecting muscle are muscle
 cramps, exercise intolerance and easy fatigability, and
 progressive weakness.Glycogen branching enzyme
 (GBE) deficiency (GSD IV, MIM #232500) is also known as
 Andersen disease. This topic will review GBE deficiency (GSD
 IV). An overview of glycogen storage disease is presented
 separately. (See "Overview of inherited disorders of
 glucose and glycogen metabolism".)PATHOGENESIS — Glycogen
 branching enzyme (GBE; amylo [1,4 to 1,6] transglucosidase)
 catalyzes the attachment of short glucosyl chains to a naked
 peripheral chain of nascent glycogen (figure 1). Deficiency
 results in abnormal structure of glycogen (similar to
 amylopectin), known as polyglucosan, with fewer branch
 points and longer alpha-1-4-linked glucose polymers.GENETICS — Glycogen
 acid (RNA) splicing [22].DIAGNOSIS — Liver
 biopsy shows excessive glycogen accumulation with a
 characteristic staining pattern. In addition to the
 normal-appearing glycogen arranged in alpha and beta
 particles, fibrillar aggregations of glycogen are detected
 by electron microscopy. Fibrosis and cirrhosis are
 invariably present in the classic form of the disease. The
 diagnosis is confirmed by absent branching enzyme activity
 in skin fibroblasts, muscle, or liver, and/or
 mutation analysis of the entire coding region of the
 glycogen branching enzyme gene (GBE1). In
 genetically confirmed cases, prenatal diagnosis can be
 performed accurately in subsequent pregnancies by analysis
 of DNA from chorionic villi or cultured amniocytes [26].
 Polyglucosan bodies (PBs) have also been detected in
 placenta at 25 and 35 weeks of gestation in two genetically
 confirmed cases, raising the possibility of prenatal
 diagnosis by histologic evaluation of placental biopsies [27].In
 patients with neuromuscular disease, the serum creatine
 kinase level is usually elevated. Muscle biopsy reveals the
 storage of periodic acid-Schiff (PAS) stain-positive
 material that resists digestion with diastase. The glycogen
 particles appear abnormal by electron microscopy, but they
 are often associated with normal beta particles.TREATMENT — No
 specific treatment is available. Liver transplantation has
 been performed with evidence of reduction in glycogen
 storage in both heart and skeletal muscle in some patients
 [28,29],
 but extrahepatic disease progression reported in other cases
 [30].
 In an in vitro study, polyglucosan neurotoxicity caused by
 glycogen branching enzyme (GBE) enzyme deficiency was
 reversed with rapamycin, indicating potential therapeutic
 value of glycogen synthase inhibition for treating glycogen
 storage disorders (GSDs) [31].SUMMARY●Glycogen
 above.)Use of



 UpToDate is subject to the Subscription
 and License Agreement.
 REFERENCES

 1

 Bao Y,
 Kishnani P, Wu JY, Chen YT. Hepatic and neuromuscular forms
 of glycogen storage disease type IV caused by mutations in
 the same glycogen-branching enzyme gene. J Clin Invest 1996;
 97:941.

 2

 Bruno
 C, van Diggelen OP, Cassandrini D, et al. Clinical and
 genetic heterogeneity of branching enzyme deficiency
 (glycogenosis type IV). Neurology 2004; 63:1053.

 3

 Bruno
 C, Cassandrini D, Assereto S, et al. Neuromuscular forms of
 glycogen branching enzyme deficiency. Acta Myol 2007;
 26:75.

 4

 Nolte
 KW, Janecke AR, Vorgerd M, et al. 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 2008;
 116:491.

 5

 de
 Moor RA, Schweizer JJ, van Hoek B, et al. Hepatocellular
 carcinoma in glycogen storage disease type IV. Arch Dis
 Child 2000; 82:479.

 6

 Moses
 SW, Parvari R. The variable presentations of glycogen
 storage disease type IV: a review of clinical, enzymatic and
 molecular studies. Curr Mol Med 2002; 2:177.

 7

 Cox
 PM, Brueton LA, Murphy KW, et al. Early-onset fetal hydrops
 and muscle degeneration in siblings due to a novel variant
 of type IV glycogenosis. Am J Med Genet 1999; 86:187.

 8

 Giuffrè
 B, Parini R, Rizzuti T, et al. Severe neonatal onset of
 glycogenosis type IV: clinical and laboratory findings
 leading to diagnosis in two siblings. J Inherit Metab Dis
 2004; 27:609.

 9

 Raju
 GP, Li HC, Bali DS, et al. A case of congenital glycogen
 storage disease type IV with a novel GBE1 mutation. J Child
 Neurol 2008; 23:349.

 10

 Tang
 TT, Segura AD, Chen YT, et al. Neonatal hypotonia and
 cardiomyopathy secondary to type IV glycogenosis. Acta
 Neuropathol 1994; 87:531.

 11

 Janecke
 AR, Dertinger S, Ketelsen UP, et al. Neonatal type IV
 glycogen storage disease associated with "null"
 mutations in glycogen branching enzyme 1. J Pediatr 2004;
 145:705.

 12

 Assereto
 S, van Diggelen OP, Diogo L, et al. Null mutations and
 lethal congenital form of glycogen storage disease type IV.
 Biochem Biophys Res Commun 2007; 361:445.

 13

 Lamperti
 C, Salani S, Lucchiari S, et al. 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 2009; 32 Suppl
 1:S161.

 14

 Escobar
 LF, Wagner S, Tucker M, Wareham J. Neonatal presentation of
 lethal neuromuscular glycogen storage disease type IV. J
 Perinatol 2012; 32:810.

 15

 Guerra
 AS, van Diggelen OP, Carneiro F, et al. A juvenile variant
 of glycogenosis IV (Andersen disease). Eur J Pediatr 1986;
 145:179.

 16

 Servidei
 S, Riepe RE, Langston C, et al. Severe cardiopathy in
 branching enzyme deficiency. J Pediatr 1987; 111:51.

 17

 Das
 BB, Narkewicz MR, Sokol RJ, et al. Amylopectinosis disease
 isolated to the heart with normal glycogen branching enzyme
 activity and gene sequence. Pediatr Transplant 2005;
 9:261.

 18

 Bruno
 C, Servidei S, Shanske S, et al. Glycogen branching enzyme
 deficiency in adult polyglucosan body disease. Ann Neurol
 1993; 33:88.

 19

 Mochel
 F, Schiffmann R, Steenweg ME, et al. Adult polyglucosan body
 disease: Natural History and Key Magnetic Resonance Imaging
 Findings. Ann Neurol 2012; 72:433.

 20

 Rifai
 Z, Klitzke M, Tawil R, et al. Dementia of adult polyglucosan
 body disease. Evidence of cortical and subcortical
 dysfunction. Arch Neurol 1994; 51:90.

 21

 Paradas
 C, Akman HO, Ionete C, et al. Branching enzyme deficiency:
 expanding the clinical spectrum. JAMA Neurol 2014;
 71:41.

 22

 Akman
 HO, Kakhlon O, Coku J, et al. Deep intronic GBE1 mutation in
 manifesting heterozygous patients with adult polyglucosan
 body disease. JAMA Neurol 2015; 72:441.

 23

 Sampaolo
 S, Esposito T, Gianfrancesco F, et al. A novel GBE1 mutation
 and features of polyglucosan bodies autophagy in adult
 polyglucosan body disease. Neuromuscul Disord 2015;
 25:247.

 24

 Wierzba-Bobrowicz
 T, Lewandowska E, Stepień T, Modzelewska J.
 Immunohistochemical and ultrastructural changes in the brain
 in probable adult glycogenosis type IV: adult polyglucosan
 body disease. Folia Neuropathol 2008; 46:165.

 25

 Massa
 R, Bruno C, Martorana A, et al. Adult polyglucosan body
 disease: proton magnetic resonance spectroscopy of the brain
 and novel mutation in the GBE1 gene. Muscle Nerve 2008;
 37:530.

 26

 Akman
 HO, Karadimas C, Gyftodimou Y, et al. Prenatal diagnosis of
 glycogen storage disease type IV. Prenat Diagn 2006;
 26:951.

 27

 Konstantinidou
 AE, Anninos H, Dertinger S, et al. Placental involvement in
 glycogen storage disease type IV. Placenta 2008; 29:378.

 28

 Matern
 D, Starzl TE, Arnaout W, et al. Liver transplantation for
 glycogen storage disease types I, III, and IV. Eur J Pediatr
 1999; 158 Suppl 2:S43.

 29

 Selby
 R, Starzl TE, Yunis E, et al. Liver transplantation for type
 IV glycogen storage disease. N Engl J Med 1991; 324:39.

 30

 Willot
 S, Marchand V, Rasquin A, et al. Systemic progression of
 type IV glycogen storage disease after liver
 transplantation. J Pediatr Gastroenterol Nutr 2010;
 51:661.

 31

 Kakhlon
 O, Glickstein H, Feinstein N, et al. Polyglucosan
 neurotoxicity caused by glycogen branching enzyme deficiency
 can be reversed by inhibition of glycogen synthase. J
 Neurochem 2013; 127:101.

 Topic
 2937 Version 10.0 • All
 rights reserved. • © 2016 UpToDate,
 Inc.

        Contributor Disclosures:
            William J Craigen, MD, PhD
                        Nothing to disclose.
            Basil T Darras, MD
                        Grant/Research/Clinical Trial Support: PTC [DMD
 (Ataluren)]; Sarepta [DMD (Eteplirsen)]. Consultant/Advisory
 Boards: Sarepta [DMD (Eteplirsen)]; Marathon, Inc [DMD
 (Deflazacort)].
            Sihoun Hahn, MD, PhD
                        Grant/Research/Clinical Trial Support: Genzyme [Pompe
 disease, registry study (Alglucosidase alpha)]; Alexion
 [Hypophosphatasia (Asfotase alpha)]; Shire [Hunter disease
 (Idursulfase)]; BioMarin [Registry study]; Shire [Registry
 study]. Consultant/advisory Boards: Shire [Hunter disease
 (Idursulfase)].
            Elizabeth TePas, MD, MS
                        Nothing to disclose.

                Contributor disclosures are reviewed for conflicts of
 interest by the editorial group. When found, these are
 addressed by vetting through a
                multi-level review process, and through requirements for
 references to be provided to support the content.
 Appropriately referenced content is
                required of all authors and must conform to UpToDate
 standards of evidence.

                Conflict
 of interest policy

        UpToDate
 Customer ServiceWolters
 Kluwer Health230
 Third Avenue
 Waltham, MA 024511.800.998.6374 (US & Canada)
 tel.+1.781.392.2000 (all other countries)
 tel.customerservice@uptodate.comwww.uptodate.com