Diagnostic Criteria for Barth syndrome

Pediatric Neurology Setting

Diagnostic Criteria for Barth Syndrome in the Pediatric Neurology Setting

- *A child with Barth syndrome could easily present in the pediatric neurologist's office for an array of reasons.*
- *A floppy infant or child may be referred to the neurologist without any other relevant background information, and may turn out to have:*
  - *Cardioskeletal myopathy*
  - *A lipid myopathy*
  - *3-methylglutaconic aciduria*
- *A geneticist, cardiologist or other specialist may refer a child to pediatric neurologist because they need his view to get a complete picture, either before or after the diagnosis has been made.*

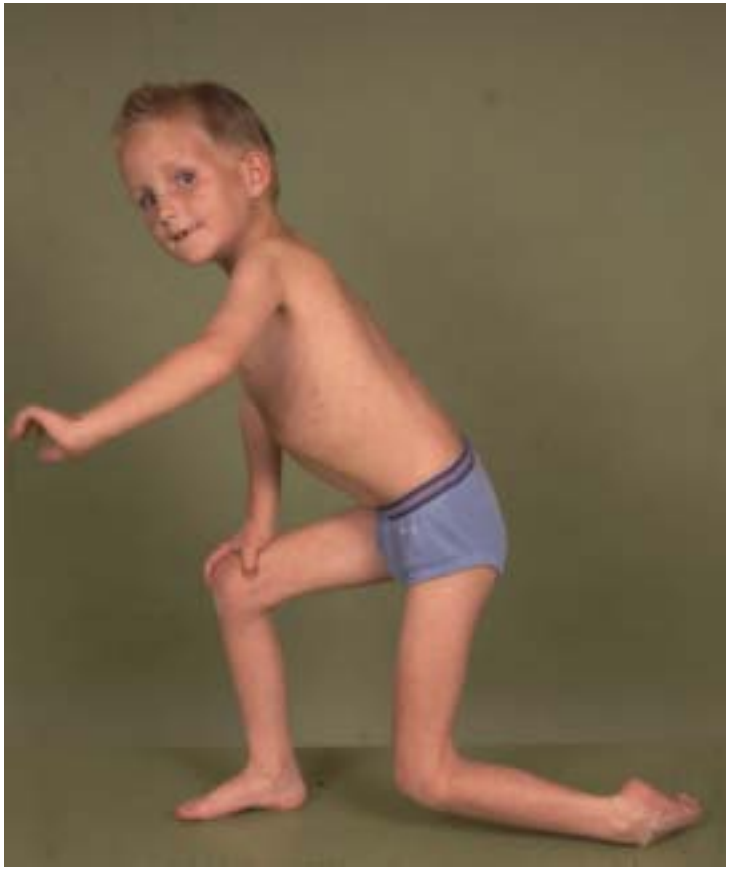
Diagnostic Criteria for Barth Syndrome in the Pediatric Neurology Setting

The neuromuscular symptoms of Barth syndrome are:

- *Muscle affection mainly in a limb girdle distribution*
- *Moderate muscle wasting*
- *Moderate weakness, permitting unsupported walking*
- *Exercise intolerance*
- *Absence of contractures*
- *No involvement of bulbar musculature, with the exception of occasional mild facial muscle weakness*
- *No progression to wheelchair dependence, no involvement of extra-ocular muscles or diaphragm.*

Diagnostic Criteria for Barth Syndrome in the Pediatric Neurology Setting

- *A child with Barth syndrome showing Gowers' sign on rising.*
- *Notice moderate muscle wasting.*

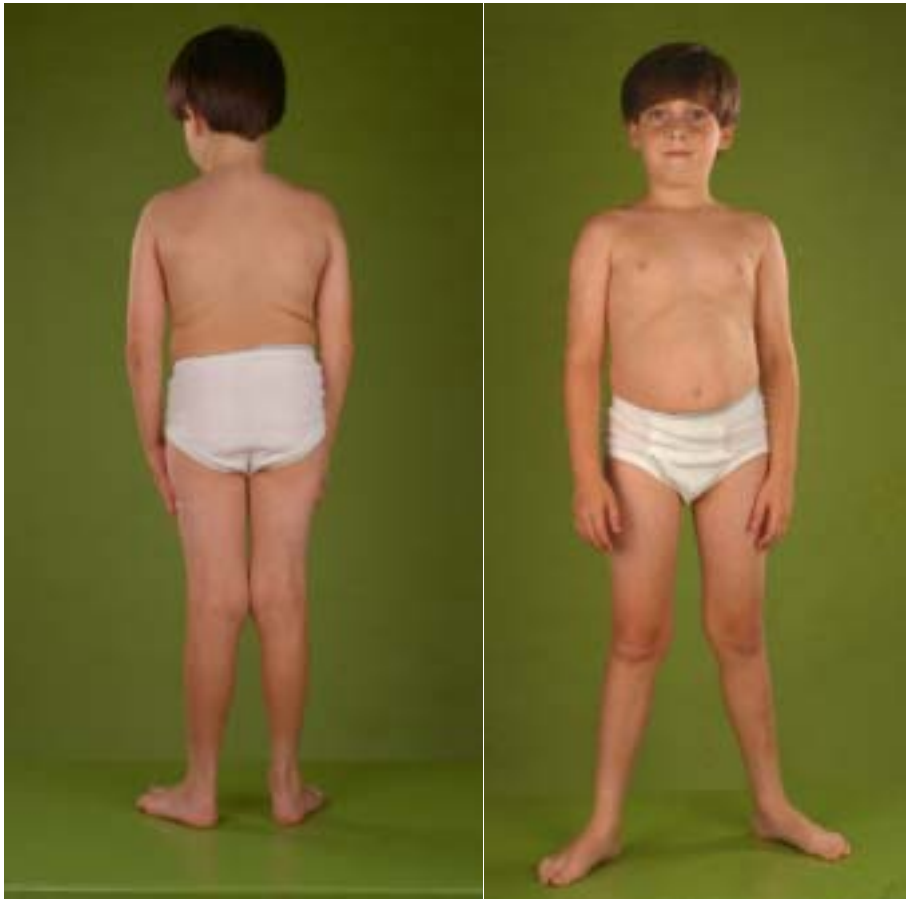


Diagnostic Criteria for Barth Syndrome in the Pediatric Neurology Setting

A boy with Barth syndrome showing

- lordotic back
- recurvated knees…….

Diagnostic Criteria for Barth Syndrome in the Pediatric Neurology Setting



- …mild wasting of extremity muscles

Diagnostic Criteria for Barth Syndrome in the Pediatric Neurology Setting

The facial appearance of Barth syndrome is not “diagnostic”, but

experienced investigators point to a similarity in facial appearance in many affected boys.

Diagnostic Criteria for Barth Syndrome in the Pediatric Neurology Setting

Cardinal Characteristics besides neuromuscular involvement:

- *Cardiomyopathy (frequently dilated)*
- *Neutropenia (chronic, cyclic or intermittent)*
- *Growth retardation (can appear as failure to thrive) before puberty*
- *3 - methylgluticonic aciduria, detectable by gaschromatography and mass-spectrometry*

Diagnostic Criteria for Barth Syndrome in the Pediatric Neurology Setting

- **Major Clinical Hazards:**
  - *Congestive heart failure*
  - *Risk of serious arrhythmia including sudden cardiac death*
  - *Serious bacterial infections*
  - *Hypoglycemia*
- **Other major problems:**
  - *Growth deficiency*
  - *Lack of stamina*

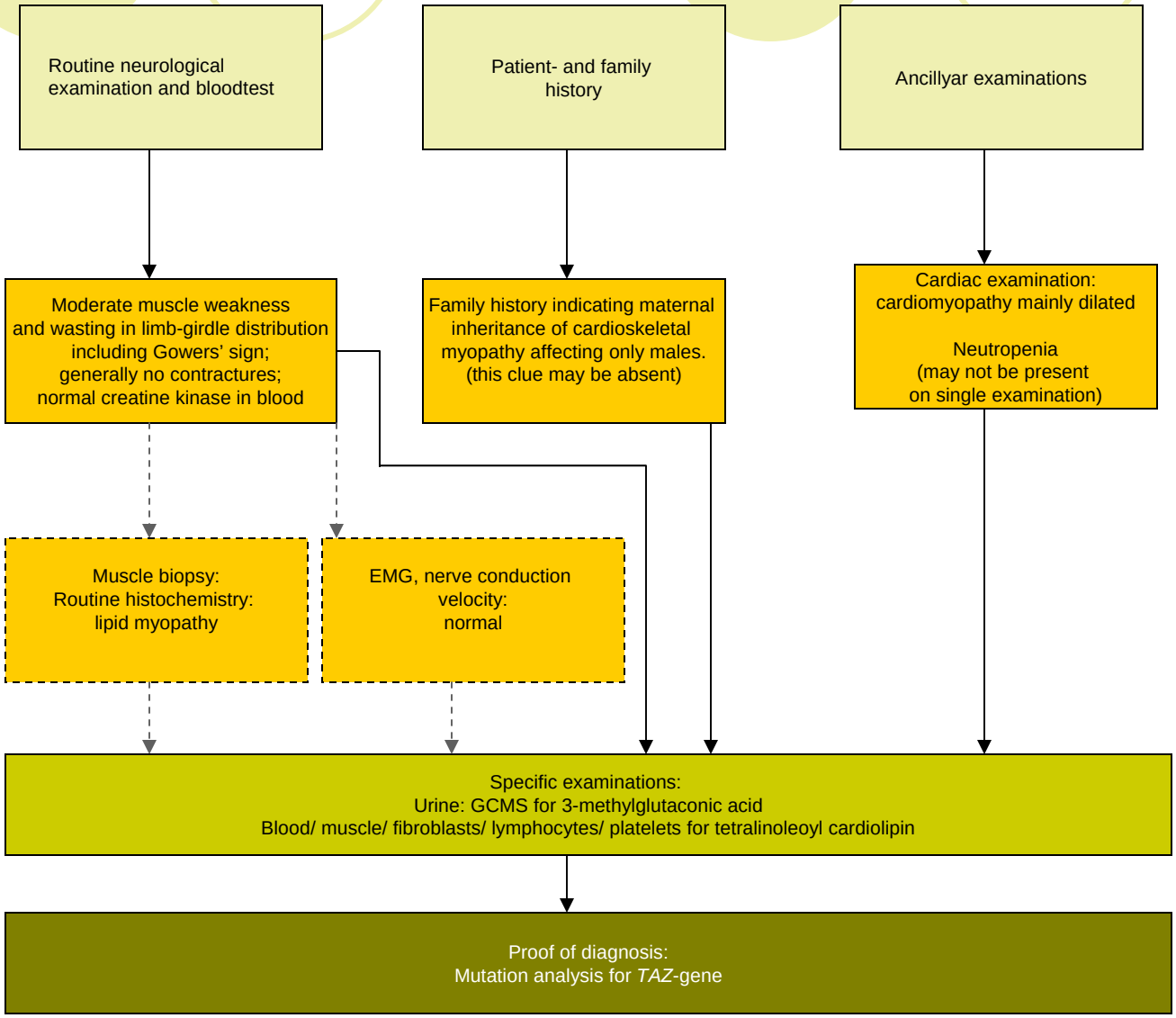
Diagnostic Criteria for Barth Syndrome in the Pediatric Neurology Setting

- **Variable Clinical Problems:**
  - *Frequent diarrhea*
  - *Recurrent aphthous ulcers*
  - *Hypoglycemia, including fasting hypoglycemia in the neonate*
  - *High incidence of minor congenital malformations*
  - *Low bone density*
  - *Reported chronic headaches and body aches especially during puberty*
  - *Feeding Problems*
  - *Reports of cognitive learning difficulties*

Diagnostic Criteria for Barth Syndrome in the Pediatric Neurology Setting

- **Diagnostic Testing**
  - *Quantitative Urine Organic Acid Analysis, including quantification of 3- methylgluticonic acid*
  - *Cardiolipin analysis of muscle, platelets, lymphocytes or cultured skin fibroblasts*
  - *DNA sequence analysis (Genetic testing of the tafazzin [G4.5] gene)*

Diagnostic flow-scheme for the diagnosis of Barth syndrome in an affected male patient



References

- *Barth PG, Wanders RJ, Vreken P, Janssen EA, Lam J, Baas F. X-linked cardioskeletal myopathy and neutropenia (Barth syndrome) (MIM 302060). J Inherit Metab Dis 1999;22(4):555-67.*
- *Kelley RI, Cheatham JP, Clark BJ, Nigro MA, Powell BR, Sherwood GW, et al. X-linked dilated cardiomyopathy with neutropenia, growth retardation, and 3-methylglutaconic aciduria. J Pediatr 1991;119(5):738-47.*
- *Cantlay AM, Shokrollahi K, Allen JT, Lunt PW, Newbury-Ecob RA, Steward CG. Genetic analysis of the G4.5 gene in families with suspected Barth syndrome [see comments]. J Pediatr 1999;135(3):311-5.*
- *Christodoulou J, McInnes RR, Jay V, Wilson G, Becker LE, Lehotay DC, et al. Barth syndrome: clinical observations and genetic linkage studies. Am J Med Genet 1994;50(3):255-64.*
- *Orstavik KH, Orstavik RE, Naumova AK, D'Adamo P, Gedeon A, Bolhuis PA, et al. X chromosome inactivation in carriers of Barth syndrome. Am J Hum Genet 1998;63(5):1457-63.*
- *Kelley RI. Quantification of 3-methylglutaconic acid in urine, plasma, and amniotic fluid by isotope-dilution gas chromatography/mass spectrometry. Clin Chim Acta 1993;220(2):157-64.*
- *Gibson KM, Elpeleg ON, Jakobs C, Costeff H, Kelley RI. Multiple syndromes of 3-methylglutaconic aciduria. Pediatr Neurol 1993;9(2):120-3.*
- *Bleyl SB, Mumford BR, Brown-Harrison MC, Pagotto LT, Carey JC, Pysher TJ, et al. Xq28-linked noncompaction of the left ventricular myocardium: prenatal diagnosis and pathologic analysis of affected individuals. Am J Med Genet 1997;72(3):257-65.*
- *Cardonick EH, Kuhlman K, Ganz E, Pagotto LT. Prenatal clinical expression of 3-methylglutaconic aciduria: Barth syndrome. Prenat Diagn 1997;17(10):983-8.*
- *Bleyl SB, Mumford BR, Thompson V, Carey JC, Pysher TJ, Chin TK, et al. Neonatal, lethal noncompaction of the left ventricular myocardium is allelic with Barth syndrome. Am J Hum Genet 1997;61(4):868-72.*
- *Chen R, Tsuji T, Ichida F, Bowles KR, Yu X, Watanabe S, et al. Mutation analysis of the G4.5 gene in patients with isolated left ventricular noncompaction. Mol Genet Metab 2002;77(4):319-25.*
- *Ichida F, Tsubata S, Bowles KR, Haneda N, Uese K, Miyawaki T, et al. Novel gene mutations in patients with left ventricular noncompaction or Barth syndrome. Circulation 2001;103(9):1256-63.*
- *Mazzocco MM, Kelley RI. Preliminary evidence for a cognitive phenotype in Barth syndrome. Am J Med Genet 2001;102(4):372-8.*

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