POMPE Diagnostic Algorithm – Infantile-onset Pompe Disease

Infantile-onset Pompe disease (IOPD) is a rare neuromuscular disorder caused by mutations in the gene that codes for acid α-glucosidase (*GAA*) and results in an accumulation of intralysosomal glycogen in the muscles and other tissues. There are recognizable forms of IOPD: the classic form characterized by a rapid onset of symptoms (within the first few months of age), cardiac and respiratory involvement with rapidly progressive decline in organ function, culminating in death by 1 year of age if left unmanaged; and there are also patients who present with signs and symptoms in infancy without the classic cardiac features of IOPD. Pompe disease can be challenging to diagnose due to its rarity, variability in symptom onset and severity, and symptom overlap with many other neuromuscular disorders. IOPD can be suspected based on signs and symptoms and confirmed through laboratory testing (measurement of GAA enzyme in various tissues, including blood), along with genetic testing revealing two pathogenic variants in the *GAA* gene.

The following diagnostic algorithm was developed by the American College of Medical Genetics Work Group on Management of Pompe Disease and can be used to confirm a diagnosis if signs and symptoms suggest IOPD (classic or non-classic).[1]

DIAGNOSTIC ALGORITHM FOR INFANTILE-ONSET POMPE DISEASE

Common Presenting Symptoms	**CARDIOVASCULAR** Cardiomegaly; Congestive heart failure; Arrhythmias such as supraventricular tachycardia; Cardiac arrest during surgery.	**PULMONARY** Frequent infections; Respiratory distress/insufficiency.	**NEUROLOGICAL** Hypotonia; Developmental delay; Gross motor delay; Loss of early motor milestones.	**GASTROINTESTINAL** Failure to thrive; Feeding difficulties.
Pertinent Patient Findings	**CARDIOVASCULAR** Murmur, gallop, pulsatile precordium, excessive sweating (cardiac related); Cardiomegaly; Cardiomyopathy; (hypertrophic +/- LVOTO) progressing to dilated cardiomyopathy.	**RESPIRATORY** Progressive respiratory involvement, nasal flaring; Use of accessory muscles, IC and SC retractions, decreased breath sounds in LLL; coarse breath sounds.	**NEUROLOGICAL** Delayed motor milestones. Hypotonia, head lag, floppy baby with ability to "slip through," frog leg position, hypertrophy of gastrocnemius muscle.	**GASTROINTESTINAL** Macroglossia, open mouth, low facial tone, decreased gag reflex, failure to thrive, poor suck and swallow, difficulty feeding with pooling of oral secretions; Hepatomegaly.

Initial Laboratory and Clinical Investigations	**CLINICAL STUDIES** Chest x-ray – cardiomegaly; EKG - huge R wave, short PR interval and broad QRS complex; Echocardiography - cardiomyopathy Electrophysiology (EMG/NCS) - myopathy.	**LABORATORY (BLOOD OR URINE)** Elevated CK, AST, ALT, LDH (in blood) Urine Hex_4 GAA activity in dried blood spots, lymphocytes, or leukocytes with blocking antibiodies to neutral maltase; Mutation testing is familial mutation known.	If GAA present, follow-up with confirmatory testing, if strong clinical suspicion. If GAA absent, obtain confirmatory studies for definitive diagnosis.
Confirmatory Studies	**DNA** *GAA* mutation testing	**ENZYMOLOGY** GAA activity testing in fibroblasts or muscle (the gold standard). Caution with muscle biopsy is needed due to anesthesia risk.	**HISTOLOGY/HISTOCHEMISTRY** Increased lysosomal glycogen. Vacuolated cells.

Please note: blood based assays are available which allow for more rapid testing and diagnostic confirmation in conjunction with *GAA* sequencing.

Abbreviations:

ALT: alanine aminotransferase; **AST:** aspartate aminotransferase; **CK:** creatine kinase; **EMG:** electromyography; **GAA:** acid α-glucosidase; **Hex_4:** hexose tetrasaccharide; **IC:** intercostal; **LDH:** lactate dehydrogenase; **LLL:** lower lung lobe; **LVOTO:** left ventricular outflow tract obstruction; **NCS:** nerve conduction study; **SC:** subcostal

References: 1. Kishnani PS, Steiner RD, Bali D, et al. Pompe disease diagnosis and management guideline. *Genet Med.* 2006;8(5):267-288.

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