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Insight into the phenotype of infants with Pompe disease identified by newborn screening with the common c.-32-13T > G "late-onset" *GAA* variant

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ABSTRACT

Objective: Newborn screening (NBS) has led to early diagnosis and early initiation of treatment for infantile onset Pompe Disease (IOPD). However, guidelines for management of late onset Pompe disease (LOPD) via NBS, especially with the IVS c.-32-13T > G are not clear. This IVS variant is noted in 68–90% cases with LOPD and has been presumed to result in "adult" disease in compound heterozygosity, with a few cases with earlier onset and a mild to no phenotype in homozygosity. Our study evaluates newborns with LOPD having IVS variant with a diligent multidisciplinary approach to determine if they have an early presentation.

Methods: Seven children with LOPD identified by NBS with IVS variant (3 compound heterozygous, and 4 homozygous) were evaluated with clinical, biochemical (CK, AST, ALT, and urinary Glc_4), cardiac evaluation, physical therapy (PT), occupational, and speech/language therapy.

Results: All seven patients demonstrated motor involvement by age 6 months; the three patients with c.-32-13 T > G variant in compound heterozygosity had symptoms as neonates. Patients with c.-32-13 T > G variant in compound heterozygosity had more involvement with persistent hyperCKemia, elevated AST and ALT, swallowing difficulties, limb-girdle weakness, delayed motor milestones, and were initiated on ERT. The patients with c.-32-13T > G variant in homozygosity had normal laboratory parameters, and presented with very subtle yet LOPD specific signs, identified only by meticulous assessments.

Conclusion: This patient cohort represents the first carefully phenotyped cohort of infants with LOPD with the "late-onset" *GAA* variant c.-32-13T > G detected by NBS in the USA. It emphasizes not only the opportunity for early detection of skeletal and other muscle involvement in infants with c.-32-13T > G variant but also a high probability of overlooking or underestimating the significance of clinically present and detectable features. It can thus serve as a valuable contribution in the development of evaluation and treatment algorithms for infants with LOPD.

1. Introduction

Pompe disease is a progressive autosomal recessive neuromuscular disorder caused by deficiency of lysosomal acid α-glucosidase (GAA) [1]. It is broadly classified into classic infantile Pompe disease (IOPD), the most severe end of the spectrum with rapidly progressive hypertrophic cardiomyopathy at birth, generalized muscle weakness, and death within the first two years of life without treatment [2,3]; and late onset Pompe disease (LOPD), encompassing childhood, juvenile, and adult-onset disease, with variable severity of muscle involvement,

Abbreviations: NBS, Newborn screening; IOPD, Infantile onset Pompe disease; LOPD, Late onset Pompe disease; GAA, Acid α-glucosidase; ERT, Enzyme replacement therapy; RUSP, Recommended uniform screening panel; CK, Creatine kinase; Glc_4, Urinary glucose tetrasaccharide; ECG, Electrocardiogram; ECHO, Echocardiogram; PT, Physical therapy; ST, Speech therapy; OT, Occupational therapy; AIMS, Alberta infant motor scale; GMFM, Gross motor function measure; VFSS, video-fluoroscopic swallow study; IT, Iliotibial; PDMS, Peabody development motor scale; ICF, International classification of function; RDCRN, Rare disease clinical research network; ORDR, Office of rare disease research; NCATS, National center for advancing translational science; NINDS, National institute of neurological disorders and stroke; NIDDK, National institute of diabetes and digestive and kidney diseases

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presenting anywhere from infancy to the sixth decade of life [4–6]. Enzyme replacement therapy (ERT) with alglucosidase alfa remains the only FDA approved treatment for Pompe disease with evidence that early initiation of treatment results in best outcomes with dramatically improved survival [7–9].

Pompe disease was added to the recommended uniform screening panel (RUSP) for newborns by the U.S. Secretary of Health and Human Services in March 2015. Currently Missouri, Illinois, New York, Kentucky, Mississippi, Ohio, Pennsylvania and Tennessee are screening for Pompe disease and many additional states are gearing towards this goal [10]. Newborn screening (NBS) has led to early diagnosis and early initiation of treatment for IOPD, as intended. However, NBS also identifies patients with "late-onset" *GAA* variants, which poses a clinical dilemma, as guidelines for management of LOPD in childhood are unclear. In the absence of NBS, early signs of LOPD such as subtle muscular weakness, swallowing difficulties, and respiratory compromise are often dismissed or overlooked as non-specific hypotonia or "developmental delay" in children, contributing to misdiagnoses and/or delayed diagnosis. NBS prevents the prolonged diagnostic odyssey for patients with LOPD, allowing for an understanding of early signs and symptoms and, thus, provides the opportunity to direct management and treatment considerations and decisions [11–14].

While immediate initiation of ERT is the standard of care for patients with variants consistent with IOPD identified by NBS, there is no consensus on if and when to initiate ERT for patients with "late-onset" *GAA* variants, especially with the leaky *GAA* splice site variant, c.-32-13T > G in intron 1 (IVS1-13T > G; IVS variant) [15]. This variant is found on at least one allele in 68–90% of Caucasian patients [16–18]. Data on the spectrum and severity of LOPD patients with c.-32-13T > G variant in homozygosity or compound heterozygosity are emerging. Patients with c.-32-13 T > G variant in compound heterozygosity and a second pathogenic variant were originally thought to have adult-onset LOPD, however the c.-32-13T > G variant has now been recognized across the disease continuum. Patients with the c.-32-13T > G variant in homozygosity have historically been thought to be asymptomatic or very mildly affected [16,19,20]. Contrary to that assumption, a recent report described six adult Pompe disease patients with c.-32-13T > G variant in homozygosity with myalgia, hyperCKaemia, and/or exercise induced fatigue, with symptom onset between 12 and 55 years [21]. The management and treatment of infants diagnosed with this "late-onset" *GAA* variant following NBS remains unclear, due to diagnostic delay and the paucity of published literature on this patient population [16,22–26]. Data from the Taiwan Pompe NBS program, which began in 2005 is a valuable resource [27–29]; however, absence of the IVS c.-32-13T > G splice site variant in Taiwan as compared to Caucasian populations, limits our ability to extrapolate conclusions from Taiwan's LOPD program [30].

We present seven consecutive patients with "late-onset" *GAA* variants identified by NBS, consisting of three patients with c.-32-13T > G variant in compound heterozygosity and a second pathogenic variant and four patients with c.-32-13T > G variant in homozygosity. The purpose of this report is to summarize the clinical presentation of these seven patients as assessed utilizing a diligent multidisciplinary approach.

2. Methods

Written informed consent was obtained from a parent or guardian for all individuals as part of Duke Institutional Review Board approved Pompe long-term follow-up study (Pro00010830) and/or Determination of CRIM status in Pompe disease (Pro00001562). Data were extracted via retrospective chart review of seven consecutive patients identified via NBS with the c.-32-13T > G splice site variant in homozygosity or compound heterozygosity (Table 1). All patients had laboratory assessments (creatine kinase (CK), urinary glucose tetrasaccharide (Glc_4), and complete metabolic profile), cardiac evaluation (electrocardiogram (ECG) and echocardiogram (ECHO)) (Table 1), genetics evaluation, physical therapy (PT) assessment, speech/language therapy (ST) and/or occupational therapy (OT) assessments as part of their evaluation at the Duke metabolic clinic (Table 2). PT assessments included qualitative assessment of posture, movement, musculoskeletal status, and standardized tests such as the Alberta Infant Motor Scale (AIMS) and Gross Motor Function Measure (GMFM). OT/ST evaluations assessed oropharyngeal muscle weakness and included video-fluoroscopic swallow study when indicated.

3. Patient reports

3.1. Patients with c.-32-13T > G variant in compound heterozygosity

3.1.1. Patient 1

Patient 1 is a Caucasian male with the c.-32-13T > G splice site variant and c.525delT (p.Glu176Argfs*45) variant, who presented with feeding difficulties, recurrent aspiration, poor weight gain, and hypotonia within a few days of life. ECHO noted a small patent foramen ovale at birth, which closed spontaneously, confirmed at age 4 months. ECG was normal. HyperCKemia was present since the early neonatal period (378 IU/L, day 8 of life; N: 60–305 IU/L), while AST and ALT were normal. Feeding assessment by Video-fluoroscopic swallow study (VFSS) performed locally at age 27 days showed moderate oropharyngeal dysphagia and poor muscle tone with a tendency for aspiration. Based on severity of his presentation, ERT at a dose of 20 mg/kg every 2 weeks was initiated at age 1 month, with joint consultation of the local physician and our team at Duke. CK levels were normalized on ERT by age 4 months (80 IU/L). Patient was first evaluated at Duke at age 7 months. PT evaluation at that time revealed generalized hypotonia with flexion/abduction/external rotation positioning of lower extremities, iliotibial (IT) band tightness, and delayed gross motor development with lack of independent sitting, AIMS score between 10th and 25th percentile, and GMFM at 23.16%. VFSS evaluation at this time revealed significant improvement in feeding ability and oropharyngeal muscle tone. At age 23 months, he had achieved significant motor milestones; started sitting with support at 10 months and without support at 12 months, pulled to stand at 12 months, walked at 15 months and could feed himself with an immature pincer grasp. Swallow study was normal. He continues to receive ERT along with physical and occupational therapy.

3.1.2. Patient 2

Patient 2 is the younger brother of Patient 1 with an identical compound heterozygous genotype. Generalized hypotonia, weak oropharyngeal skills and poor suck were present since birth. The patient also had hyperCKemia (435 IU/L, day of life 4) and normal urinary Glc_4 level. Similar to his brother, ECHO at birth revealed a patent foramen ovale, which resolved spontaneously. ECG and ECHO have been unremarkable since. The local physician consulted with our team on this patient. Given the early clinical symptoms and family history of Pompe disease, it was jointly decided to initiate ERT on day 35 of life at a dose of 20 mg/kg every 2 weeks. Medical evaluation at Duke at age 2 months noted generalized hypotonia with facial myopathy, and delayed gross motor milestones. PT evaluation at age 2 months revealed flexion/abduction/external rotation positioning of lower extremities with tightness bilaterally in hip flexors, hamstrings, and IT bands. He had a tendency to remain on toes when held in supported standing with additional support required for weight bearing through lower extremities. He had decreased head control for age, reflecting hypotonia/decreased neck strength. He also had difficulty lifting his head in prone, with asymmetric head lift to 45 degrees, and an inability to maintain head in midline when supine. AIMS score at age 2 months was between 10-25th percentile. Continued ERT and PT/OT were recommended.