ADVANCES IN DIAGNOSIS AND MANAGEMENT OF POMPE DISEASE

James E. Davison*

Metabolic Medicine, Great Ormond Street Hospital for Children, NHS Foundation Trust, London, UK

Abstract

Pompe disease is an autosomal recessive lysosomal glycogen storage disorder caused by the deficiency of acid alpha-glucosidase and subsequent progressive glycogen accumulation due to mutations in the GAA gene. Pompe disease manifests with a broad spectrum of disease severity, ranging from severe infantile-onset diseases such as hypotonia and hypertrophic cardiomyopathy to late-onset diseases such as myopathy and respiratory compromise. The diagnosis requires demonstration of deficiency of the lysosomal acid alpha-glucosidase enzyme, which can be assayed in dried blood spot or liquid blood samples, together with supportive biomarker tests, and confirmed with molecular genetic analysis. Targeted screening of at-risk populations and universal newborn screening can result in earlier diagnosis and enable earlier treatment initiation, which result in the potential improvement of clinical outcomes. Disease-modifying treatment with enzyme replacement therapy has partially altered the natural history of the disease, but more efficacious novel therapies are under evaluation including second-generation enzyme replacement therapies, molecular chaperones and gene therapy approaches. Long-term survivors with Pompe disease are now manifesting novel aspects of the disease including widespread vascular disease, smooth muscle and central nervous system involvement, and these emerging phenotypes will require additional specific therapeutic approaches.

Keywords

Pompe disease, enzyme replacement therapy, gene therapy

Introduction

Pompe disease (MIM # 232300) is an autosomal recessive lysosomal glycogen storage disorder first described in 1932 (1) and it is caused by biallelic mutations in the GAA gene (MIM 606800) that encodes the lysosomal enzyme acid alpha-1,4-glucosidase (GAA; EC 3.2.1.20), also known as acid maltase. GAA has a cellular housekeeping function in the lysosomal degradation of glycogen. The deficiency of GAA results in progressive storage and accumulation of glycogen, initially within the lysosome but subsequently within the cytoplasm and into muscle inter-fibre free glycogen pools causing severe damage to the normal muscle ultrastructure and its function (2). While Pompe disease is predominantly a disorder of muscle affecting both skeletal and cardiac muscle, there are emerging non-muscle phenotypes with other tissues getting affected, which include smooth muscle of gastrointestinal tract and blood vessels, bone, and peripheral nervous system and central nervous system (CNS), resulting in multiple novel manifestations (3). Pompe disease consists of a spectrum of phenotypic diseases ranging from severe infantile-onset Pompe disease that manifests in early infancy with hypotonia, respiratory insufficiency and hypertrophic cardiomyopathy and natural history of rapid progression with death occurring at 12 months (4) to late-onset Pompe disease that can manifest with myopathy affecting gait and mobility and respiratory decline as late as 7th or 8th decade of life, but without significant cardiomyopathy (5, 6). Pompe disease may be diagnosed as an incidental or unsuspected finding during the investigation of “hyper-creatine kinase-aemia” or other unexplained elevated serum enzymes including lactate dehydrogenase or the ‘liver enzymes’ aspartate/alanine aminotransferase that are liberated from the damaged muscle tissue (7). The clinical spectrum reflects the degree of any residual GAA
enzyme activity, and accordingly the combination of severe or less severe mutations occurs leading to a relatively strong genotype–phenotype correlation (8, 9).

**Diagnostics**

The cornerstone of the diagnosis of Pompe disease remains to be enzymology, which demonstrates a deficiency in the activity of the lysosomal GAA. Historically this test was conducted in fresh muscle samples or cultured skin fibroblasts, but with minimally invasive testing on lymphocyte or leucocyte (liquid blood) assays or in dried blood spot samples in the first line investigation (10, 11). The assay in leucocytes and dried blood spot samples is complicated by interference from non-lysosomal maltase glucoamylase, and so it requires the use of inhibitors such as acarbose and assays at neutral and acidic pH to derive the required test sensitivity and specificity. The finding of abnormal enzyme activity on the blood spot assay requires second-tier confirmation using enzymology in another sample type, supportive assays and molecular genetic testing. The enzyme diagnosis can be supported by histological findings on examination of a blood film for periodic acid-Schiff stain (PAS)-positive vacuolated lymphocytes (12, 13) and by elevated urine glucose tetrasaccharide levels (14). Molecular genetic analysis for mutations in GAA will confirm the diagnosis. There are more than 500 described mutations, with some frequent alleles including the IVS splice site mutation c.-32-13T>G associated with late-onset disease (15), a common Taiwanese mutation (resulting in p.Asp645Glu) (16) and p.Arg854X frequent in African/African-American populations.

Patients with severe infantile-onset Pompe disease can be differentiated into two groups: one group with detectable GAA protein (Cross Reactive Immunologic Material Positive, CRIM+) and another group without any detectable GAA protein (Cross Reactive Immunologic Material Negative, CRIM−). The CRIM− cohort has a worse prognosis and response to treatment with enzyme replacement therapy, which is at least in part due to the generation of high titre anti-drug antibodies by the patient’s immune system that was not exposed to the GAA protein during early immune tolerisation (17). This necessitates modifications to treatment. The CRIM status can be determined by prediction from the genotype if it is known (18) or from a rapid-turnaround blood-based assay in leucocytes (19). Diagnostic algorithms for infantile (20) and late (21) onset Pompe diseases have been established.

**Early Diagnosis**

There is emerging evidence that early diagnosis and initiation of treatment result in an improved clinical outcome (22–24). The ready availability of a simple screening test, i.e. dried blood spot testing, means that any at-risk patient with any potential ‘red flag’ signs that could suggest Pompe disease may be tested. This will include all hypotonic infants especially if they also have cardiomyopathy, children with unexplained motor delay and older patients with exertional myalgia, fatigue and also those with unexplained elevated ‘liver enzymes’ or serum CK, those with a limb-girdle syndrome or unexplained respiratory insufficiency.

Also, targeting such ‘at risk’ populations, universal newborn screening (NBS) for Pompe disease has been initiated in several countries (25). Diagnosis from NBS enables identification of patients with infantile-onset Pompe disease, and rapid initiation of early treatment including immunosuppressive treatment for CRIM− patients. After the detection from NBS programs, patients are treated and they show improved long-term clinical outcomes with significantly improved overall and ventilator-free survival, albeit in a population of entirely CRIM+ patients (26). However, the identification of late-onset (or very late-onset) Pompe disease patients from NBS is problematic, raising questions around treatment initiation, and impact on health/life insurance.

Protocols for managing patients identified from NBS have been proposed (27, 28).

**Treatment**

The management of a patient with Pompe disease requires an extensive multidisciplinary team to address the multisystem manifestations, including cardiology, respiratory, speech and language (swallow), physiotherapy/neurology, genetics and metabolic physicians. Many patients require mobility support and many need non-invasive respiratory support.

Pompe disease is a progressive disorder, but disease-modifying treatments using enzyme replacement therapy are now common in clinical use. Enzyme replacement therapies for lysosomal storage disorder depend on the cross-correction principle, with the uptake of circulating enzyme protein into cells and trafficking to the lysosome via the mannose-6-phosphate signalling system (29). The first human patient was treated with recombinant enzyme replacement 20 years ago (30), and subsequent phase I/II studies (31) led to the market authorisation of alglucosidase alfa (Myozyme ®, Genzyme) in 2006. Subsequent studies have confirmed the effect of this treatment ameliorating the natural history of infantile-onset (32) and late-onset (33, 34) Pompe diseases.

However, current enzyme replacement therapy is not curative. Patients still display a significant burden of morbidity mandating improvements in current disease-modifying treatment, and novel emerging aspects of the long-term phenotype in patients receiving enzyme replacement therapy require new approaches to address these issues. Factors that are known to affect the outcome and efficacy of enzyme replacement therapy include the CRIM status of infantile-onset patients, the
generation of anti-drug antibodies, the degree of (irreversible) muscle damage when treatment is initiated, and concordantly the age and clinical status at the start of treatment (32).

Novel Disease-Modifying Therapies
Several approaches to improve the efficacy of treatment are under investigation. Increased dose and frequency of enzyme replacement therapy appear to increase efficacy, with some centres using 40 mg/kg weekly dosing of alglucosidase alfa for infantile-onset Pompe disease (Van den Hout, personal communication). For CRIM- infantile-onset Pompe disease patients, immunomodulation at the time of enzyme replacement therapy initiation has been shown to decrease the generation of high-titre anti-drug antibodies and improve the clinical outcomes (35, 36) and necessitates the determination of CRIM status in all newly diagnosed infantile-onset Pompe disease patients. Approaches to increasing muscle uptake of the recombinant enzyme have included exercise regimens during infusions and the use of beta-agonists (37, 38). Several next-generation enzyme replacement therapies are being evaluated that aim to improve muscle-specific uptake by a range of molecular mechanisms, such as increased mannose-6-phosphate tagging or utilising other uptake mechanisms, including in both late-onset [e.g. clinical trials (see (39) for details of trials) NCT02898753, NCT01230801, NCT02782741] and infantile-onset (NCT03019406) cohorts, as well as studies evaluating chaperone therapies in conjunction with highly targeted intravenous enzyme replacement therapies (NCT02675465/NCT04138277). All enzyme replacement therapies require repeated life-long dosing, and so gene therapy approaches are an effective alternative treatment method. These aim to introduce functioning copies of the GAA gene that can be transcribed and translated to produce the GAA enzyme continuously, which can then undergo the normal post-translation modification and processing and trafficking to the lysosome. Approaches include targeting the liver with AAV-vector carried GAA gene, utilising the liver as an ‘enzyme factory’ (40, 41) in phase i trial in late-onset patients (NCT03533673), or directly targeting muscle tissues (42) (e.g. NCT02240407).

Monitoring Disease Progression and Treatment Efficacy
The long-term monitoring of patients with Pompe disease, immunomodulation at the time of enzyme replacement therapy initiation has been shown to decrease the generation of high-titre anti-drug antibodies and improve the clinical outcomes (35, 36) and necessitates the determination of CRIM status in all newly diagnosed infantile-onset Pompe disease patients. Approaches to increasing muscle uptake of the recombinant enzyme have included exercise regimens during infusions and the use of beta-agonists (37, 38). Several next-generation enzyme replacement therapies are being evaluated that aim to improve muscle-specific uptake by a range of molecular mechanisms, such as increased mannose-6-phosphate tagging or utilising other uptake mechanisms, including in both late-onset [e.g. clinical trials (see (39) for details of trials) NCT02898753, NCT01230801, NCT02782741] and infantile-onset (NCT03019406) cohorts, as well as studies evaluating chaperone therapies in conjunction with highly targeted intravenous enzyme replacement therapies (NCT02675465/NCT04138277). All enzyme replacement therapies require repeated life-long dosing, and so gene therapy approaches are an effective alternative treatment method. These aim to introduce functioning copies of the GAA gene that can be transcribed and translated to produce the GAA enzyme continuously, which can then undergo the normal post-translation modification and processing and trafficking to the lysosome. Approaches include targeting the liver with AAV-vector carried GAA gene, utilising the liver as an ‘enzyme factory’ (40, 41) in phase i trial in late-onset patients (NCT03533673), or directly targeting muscle tissues (42) (e.g. NCT02240407).
onset Pompe disease, which manifests as progressive abnormalities on MRI brain imaging (56), sensorineural hearing loss (57, 58) and impaired function with abnormalities of processing speed and emergent learning difficulties (3, 59, 60). There is also evidence of potential cognitive dysfunction in patients with late-onset Pompe disease (61) although these patients do not seem to have the same progressive white matter disease as seen in the infantile cohort, probably reflecting the degree of residual enzyme activity and multifactorial causes for the CNS disease(62). Conventional intravenous enzyme replacement therapies and the therapies that are presently under development are not expected to cross the blood–brain barrier and are therefore unlikely to be effective in ameliorating the CNS component of Pompe disease. Similarly, gene therapies that aim to target muscles or utilise the liver as a production source of the enzyme may not be effective in treating the brain, and so CNS-targeted therapies are must for effective treatment (63).

Conclusion

Rapid progress has been made in the understanding of the pathophysiology of Pompe disease, and exciting developments in disease-modifying therapies are under evaluation. An earlier diagnosis may be facilitated by targeted or universal screening, but appropriate guidelines for the monitoring and management, including specific therapy initiation, of patients identified through such screening is required. New approaches to evaluating novel therapies, including methods such as quantitative MRI or biomarkers such as miRNAs for evaluating serial changes in muscle function may guide future therapeutic protocols. The emergence of novel phenotypic aspects of Pompe disease in long-term survivors who are treated with first-generation enzyme replacement therapy requires appropriate monitoring and further development of tissue-specific targeted supportive and disease-modifying therapies.

Author Contributions

JD drafted the manuscript and takes full responsibility for its contents. Our article is not published in any other journal and not in consideration for publication by any other journal.

Conflict of Interest

JD has received honoraria from Sanofi Genzyme for educational speaking engagements and is a principal investigator (unpaid) on the clinical trial of alglucosidase alfa in children (NCT03019406).

ORCID Identifier of the Author

James Davison 0000-0002-9009-5538 (https://orcid.org/0000-0002-9009-5538).

References

1. Pompe JC. Over idiopathische hypertrofie van het hart. Ver-eenigingsverslag van het Genootschap ter bevordering van Natuur-, Genees- en Heelkunde te Amsterdam. Vergadering van de afdeling Geneeskunde, op woensdag 18 November 1931. Ned Tijdschr Geneeskd. 1932;76:304–11.
2. Thurberg BL, Lynch Maloney C, Vaccaro C, Afonso K, Tsai AC, Bossen E, et al. Characterization of pre- and post-treatment pathol-ogy after enzyme replacement therapy for Pompe disease. Lab Invest. 2006;86(12):1208–20. doi: 10.1038/labinvest.3700484
3. Hahn A, Schänzer A. Long-term outcome and unmet needs in infantile-onset Pompe disease. Ann Transl Med. 2019;7(13):283. doi: 10.21037/atm.2019.04.70
4. van den Hout HM, Hop W, van Diggelen OP, Smeitink JA, Smit GP, Poll-The BT, et al. The natural course of infantile Pompe’s disease: 20 original cases compared with 133 cases from the literature. Pediatrics. 2003;112(2):332–40. doi: 10.1542/peds.112.2.332
5. Gungör D, de Vries JM, Hop WC, Reuser AJ, van Doorn PA, van der Ploeg AT, et al. Survival and associated factors in 268 adults with Pompe disease prior to treatment with enzyme replacement therapy. Orphanet J Rare Dis. 2011;6:34. doi: 10.1186/1750-1172-6-34
6. Hagemans ML, Winkel LP, Van Doorn PA, Hop WJ, Loonen MC, Reuser AJ, et al. Clinical manifestation and natural course of late-onset Pompe’s disease in 54 Dutch patients. Brain. 2005;128(Pt 3):671–7. doi: 10.1093/brain/awh384
7. Lukacs Z, Nieves Cobos P, Wenninger S, Willis TA, Guglieri M, Roberts M, et al. Prevalence of Pompe disease in 3,076 patients with hyperCKemia and limb-girdle muscular weakness. Neurology. 2016;87(3):295–8. doi: 10.1212/wnl.0000000000002758
8. Fukuhara Y, Fuji N, Yamazaki N, Hirakiyama A, Kamioka T, Seo JH, et al. A molecular analysis of the GAA gene and clinical spec-trum in 38 patients with Pompe disease in Japan. Mol Genet Metab Rep. 2017;14:3–9. doi: 10.1016/j.ymgmr.2017.10.009
9. Pompe disease GAA variant database. Available from: http://www.pompevariantdatabase.nl/pompe_mutations_list.php?orderby=aMut_ID1
10. Goldstein JL, Young SP, Changela M, Dickerson GH, Zhang H, Dai J, et al. Screening for Pompe disease using a rapid dried blood spot method: experience of a clinical diagnostic laboratory. Muscle Nerve. 2009;40(1):32–6. doi: 10.1002/mus.21376
11. Kishnani PS, Amantino HM, Lindberg C, Miller TM, Wilson A, Keutzer J. Methods of diagnosis of patients with Pompe disease: data from the Pompe Registry. Mol Genet Metab. 2014;113(1–2):84–91. doi: 10.1002/mge.21376
12. Anderson G, Smith VV, Malone M, Sebire NJ. Blood film exam-i nation for vacuolated lymphocytes in the diagnosis of metabolic disorders; retrospective experience of more than 2,500 cases from a single centre. J Clin Pathol. 2005;58(12):1305–10. doi: 10.1136/jcp.2005.027045
24. Schoser B, Stewart A, Kanters S, Hamed A, Jansen J, Chan K, et al. Survival and long-term outcomes in late-onset Pompe disease following alglucosidase alfa treatment: a systematic review and meta-analysis. J Neurol. 2017;264(4):621–30. doi: 10.1007/s00415-016-8219-8

25. Bodamer OA, Scott CR, Giugliani R; Pompe Disease Newborn Screening Working Group. Newborn screening for Pompe disease. Pediatrics. 2017;140(Suppl 1):S4–13. doi: 10.1542/peds.2016-0280C

26. Chien YH, Lee NC, Chen CA, Tsai FJ, Tsai WH, Shieh JY, et al. Long-term prognosis of patients with infantile-onset Pompe disease diagnosed by newborn screening and treated since birth. J Pediatr. 2015;166(4):985.e1–2–91.e1-2. doi: 10.1016/j.jpeds.2014.10.068

27. Kronn DF, Day-Salvatore D, Hwu WL, Jones SA, Nakamura K, Okuyama T, et al. Management of confirmed newborn-screened patients with Pompe disease across the disease spectrum. Pediatrics. 2017;140(Suppl 1):S24–45. doi: 10.1542/peds.2016-0280E

28. Khanani PS, Hwu WL; Pompe Disease Newborn Screening Working Group. Introduction to the newborn screening, diagnosis, and treatment for Pompe disease guidance supplement. Pediatrics. 2017;140(Suppl 1):S1–3. doi: 10.1542/peds.2016-0280B

29. Thomas R, Kermode AR. Enzyme enhancement therapeutics for lysosomal storage diseases: Current status and perspectives. Mol Genet Metab. 2019;126(2):83–97. doi: 10.1016/j.ymgme.2018.11.011

30. Van den Hout H, Reuser AJ, Vulto AG, Loonen MC, Cromme-Dijkstra A, Van der Ploeg AT. Recombinant human alpha-glucosidase from rabbit milk in Pompe patients. Lancet. 2000;356(9227):397–8. doi: 10.1016/s0140-6736(00)02533-2

31. Amalfitano A, Bengur AR, Morse RP, Majure JM, Case LE, Veerling DL, et al. Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: results of a phase III clinical trial. Genet Med. 2001;3(2):132–8. doi: 10.1038/gim200127

32. Broomfield A, Fletcher J, Davison J, Finnegan N, Fenton M, Chikermane A, et al. Response of 33 UK patients with infantile-onset Pompe disease to enzyme replacement therapy. J Inherit Metab Dis. 2016;39(2):261–71. doi: 10.1007/s10545-015-9898-5

33. van der Ploeg AT, Clemens PR, Corzo D, Escolar DM, Florence J, Groeneveld GJ, et al. A randomized study of alglucosidase alfa in late-onset Pompe’s disease. N Engl J Med. 2010;362(15):1396–406. doi: 10.1056/NEJMoa0908659

34. Kuperus E, Krijnshaar ME, Wens SCA, de Vries JM, Favejee MM, van der Meijden JC, et al. Long-term benefit of enzyme replacement therapy in Pompe disease: a 5-year prospective study. Neurology. 2017;89(23):2365–73. doi: 10.1212/WNL.0000000000004711

35. Kazi ZB, Desai AK, Berrier KL, Troxler RB, Wang YR, Abdul-Rahman OA, et al. Sustained immune tolerance induction in enzyme replacement therapy-treated CRIM-negative patients with infantile Pompe disease. JCI Insight. 2017;2(16):e94328. doi: 10.1172/jci.insight.94328

36. Messinger YH, Mendelsohn NJ, Rhead W, Dimmock D, Hershkovitz E, Champion M, et al. Successful immune tolerance induction to enzyme replacement therapy in CRIM-negative infantile Pompe disease. Genet Med. 2012;14(1):135–42. doi: 10.1038/gim.2011.4
37. Koeberl DD, Austin S, Case LE, Smith EC, Buckley AF, Young SP, et al. Adjunctive albuterol enhances the response to enzyme replacement therapy in late-onset Pompe disease. FASEB J. 2014;28(5):2171–6. doi: 10.1096/fj.13-241893
38. Chien YH, Hwu WL, Lee NC, Tsai FJ, Koeberl DD, Tsai WH, et al. Albuterol as an adjunctive treatment to enzyme replacement therapy in infantile-onset Pompe disease. Mol Genet Metab Report. 2017;11:31–5. doi: 10.1016/j.ymgmr.2017.04.004
39. NIH. Clinical Trials Database. Available from: www.clinicaltrials.gov.
40. Puzzo F, Colella P, Biferi MG, Bali D, Paulk NK, Vidal P, et al. Rescue of Pompe disease in mice by AAV-mediated liver delivery of secretable acid α-glucosidase. Sci Transl Med. 2017;9(418):eaam6375. doi: 10.1126/scitranslmed.aam6375
41. Kishnani PS, Koeberl DD. Liver depot gene therapy for Pompe disease. Ann Transl Med. 2019;7(13):288. doi: 10.21037/atm.2019.05.02
42. Ronzitti G, Collaud F, Laforet P, Mingozzi F. Progress and challenges of gene therapy for Pompe disease. Ann Transl Med. 2019;7(13):287. doi: 10.21037/atm.2019.04.67
43. Swift G, Cleary M, Grunewald S, Lozano S, Ryan M, Davi J. Swallow prognosis and follow-up protocol in infantile-onset Pompe disease. JIMD Rep. 2017;33:11–7. doi: 10.1007/9804_2016_576
44. Figueroa-Bonaparte S, Llauger J, Segovia S, Belmonte I, Pedrosa I, Montiel E, et al. Quantitative muscle MRI to follow up late onset Pompe patients: a prospective study. Sci Rep. 2018;8(1):10898. doi: 10.1038/s41598-018-29170-7
45. Tarallo A, Carissimo A, Gatto F, Nusco E, Toscano A, Musumeci O, et al. microRNAs as biomarkers in Pompe disease. Genet Med. 2019;21(3):591–600. doi: 10.1038/s41436-018-0103-8
46. Carrasco-Rozas A, Fernández-Simón E, Lleixà MC, Belmonte I, Pedrosa-Hernandez I, Montiel-Morillo I, et al. Identification of serum microRNAs as potential biomarkers in Pompe disease. Ann Clin Transl Neurol. 2019;6(7):1214–24. doi: 10.1002/acn.30800
47. Schüller A, Wenninger S, Strigl-Pill N, Schoser B. Toward deconstructing the phenotype of late-onset Pompe disease. Am J Med Genet C Semin Med Genet. 2012;163:1163–72. doi: 10.1002/ajmg.c.31322
48. Chan J, Desai AK, Zaki ZB, Corey K, Austin S, Hobson-Webb LD, et al. The emerging phenotype of late-onset Pompe disease: a systematic literature review. Mol Genet Metab. 2017;120(3):163–72. doi: 10.1016/j.ymge.2016.12.004
49. Mori M, Bailey LA, Estrada J, Rehder CW, Li JS, Rogers JG, et al. Severe cardiomyopathy as the isolated presenting feature in an adult with late-onset Pompe disease: a case report. JIMD Rep. 2017;31:79–83. doi: 10.1007/8904_2016_563
50. Bernstein DL, Bialer MG, Mehta L, Desnick RJ. Pompe disease: dramatic improvement in gastrointestinal function following enzyme replacement therapy. Report of three late-onset patients. Mol Genet Metab. 2010;101(2–3):130–3. doi: 10.1016/j.ymgme.2010.06.003.
51. Ajay D, McNamara ER, Austin S, Wiener JS, Kishnani P. Lower urinary tract symptoms and incontinence in children with Pompe disease. JIMD Rep. 2016;28:59–67. doi: 10.1007/8904_2015_492
52. Guevara-Campos J, González-Guevara L, Cauli O. Skeletal alterations, developmental delay and new mutations in juvenile-onset Pompe disease. Neuromuscul Disord. 2019;29(3):192–7. doi: 10.1016/j.nmd.2018.11.013
53. Hensel O, Hanisch F, Stock K, Stoevesandt D, Deschauer M, Müller T. Morphology and function of cerebral arteries in adults with Pompe disease. JIMD Rep. 2015;20:27–33. doi: 10.1007/8904_2014_385
54. Quenardelle V, Bataillard M, Bazin D, Lannes B, Wolff V, Echaniz-Laguna A. Pompe disease presenting as an isolated generalized dilative arteriopathy with repeated brain and kidney infaracts. J Neurol. 2015;262(2):473–5. doi: 10.1007/s00415-014-7582-6
55. Pena LD, Proia AD, Kishnani PS. Postmortem findings and clinical correlates in individuals with infantile-onset Pompe disease. JIMD Rep. 2015;23:45–54. doi: 10.1007/8904_2015_426
56. Broomfield A, Fletcher J, Hensman P, Wright R, Prunty H, Pavaine J, et al. Rapidly progressive white matter involvement in early childhood: the expanding phenotype of infantile onset Pompe? JIMD Rep. 2018;39:55–62. doi: 10.1007/8904_2017_46
57. van Capelle CI, Goegebeure A, Homans NC, Hoeve HL, Reuser AJ, van der Ploeg AT. Hearing loss in Pompe disease revisited: results from a study of 24 children. J Inherit Metab Dis. 2010;33(5):597–602. doi: 10.1007/s10545-010-9144-0
58. Kamphoven JH, de Ruiter MM, Winkel LP, Van den Hout HM, Bijman J, De Zeeuw CI, et al. Hearing loss in infantile Pompe’s disease and determination of underlying pathology in the knockout mouse. Neurobiol Dis. 2004;16(1):14–20. doi: 10.1016/j.nbd.2003.12.018
59. Ebbink BJ, Poelman E, Aarsen FK, Plug I, Régal L, Munters C, et al. Classic infantile Pompe patients approaching adulthood: a cohort study on consequences for the brain. Dev Med Child Neurol. 2018;60(6):579–86. doi: 10.1111/dmcn.13740
60. Spiridigliozzi GA, Keeling LA, Stefanescu M, Li C, Austin S, Kishnani PS. Cognitive and academic outcomes in long-term survivors of infantile-onset Pompe disease: a longitudinal follow-up. Mol Genet Metab. 2017;121(2):127–37. doi: 10.1007/s10597-017-3808-y
61. Musumeci O, Marino S, Granata F, Morabito R, Bonanno L, Brizzi M, et al. Central nervous system involvement in late-onset Pompe disease: clues from neuroimaging and neuropsychological analysis. Eur J Neurol. 2019;26(3):442–51, e34–5. doi: 10.1111/dmcn.13835
62. Schneider I, Hensel O, Zierer S. White matter lesions in treated adults with Pompe disease. JIMD Rep. 2015;23:45–54. doi: 10.1007/8904_2015_426
63. Byrne BJ, Fuller DD, Smith BK, Clement N, Coleman K, Cleaver B, et al. Pompe disease gene therapy: neural manifestations require consideration of CNS directed therapy. Ann Transl Med. 2019;7(13):290. doi: 10.21037/atm.2019.05.56