Neurology Asia 2025; 30(3) : 951 – 952

CORRESPONDENCE

Late-onset Pompe disease: Experience from Western India over 25 years

We wish to report the clinical and genetic profile of 10 patients with late-onset Pompe disease (LOPD) from the Western part of India. The prevalent diagnostic delay despite improvements in investigative modalities, phenotypic variations and the genotypic details are discussed.

This long-term data collected over 26 years helped us to observe the landscape of the investigations in LOPD. Our centre catered to the patients mainly from Maharashtra, Madhya Pradesh, Gujarat and Rajasthan in West India. The initial patients before the year 2000 were primarily diagnosed with the help of muscle biopsy. Two of these were from a cohort of unclassified limb girdle muscular dystrophies, who underwent muscle biopsy as a part of evaluation, which showed PAS positive, diastase sensitive glycogen inclusions and were diagnosed with LOPD. Subsequently, with availability of GAA enzyme assays (lymphocytes and leucocytes) and GAA enzyme activity on dried blood spots in early 2000s, these tests were additionally utilized due to the non-invasive nature of these tests. Shortly after, next generation sequencing stormed the region and was employed as a confirmatory test in our cohort. So, the diagnostic methodologies varied in this cohort, as they evolved over time.

A total of 2,374 patients presenting with a clinical syndrome of myopathy were evaluated in this study period of 26 years. 10 patients (0.42%) were diagnosed with LOPD. All patients were of Indian ethnicity. Four patients were born of consanguineous marriage, and three patients had an affected family member. Mean age at the time of diagnosis was 25.4 years while mean age of symptom onset was 19.3 years (1-37 years). Six patients presented with a limb girdle type of weakness, predominantly affecting the pelvic girdle. Two patients presented with acute respiratory distress and required mechanical ventilation, while respiratory symptoms gradually affected a total of 7 patients. A single patient had facial weakness and scapular winging at presentation along with proximal muscle weakness and 1 had myalgia and exercise intolerance. Scapular winging and facial weakness has been infrequently reported in the literature.[1] The most common phenotype reported in literature is limb girdle weakness, which was also seen in our cohort. Atypical phenotypes reported in LOPD include- cardiac conduction abnormalities like WPW syndrome, hearing loss, rigid spine syndrome.[2] These were not seen in our patients. There was a mild to moderate elevation in CK levels (492-2000 IU). Electrophysiology showed myopathic units with prominent spontaneous activity in form of fibrillation potentials, and pseudo-myotonic discharges in paraspinal muscles. To note, the prominent myotonic discharges found in one patient initially led to the misdiagnosis as myotonic dystrophy. GAA enzyme activity was not detected in one of our patients while 5 patients had very low enzyme activity. Muscle biopsy from quadriceps showed PAS positive inclusions in 7 patients and was normal in 1 patient.

Clinical exome sequencing was available in 7 patients. The most prevalent pathogenic variant in our patients was c.1841C>T (p.T614M) in exon 13 of GAA gene (4 patients). This missense variant is previously reported in the Indian as well as Caucasian populations.[3] An intronic splice site variant c-32-13T>G, the most reported variant globally and maximally found in the Caucasian population[4] was present in one of our patients. This intronic variant results in splicing out of exon 2 during GAA mRNA expression forming a non-functional protein.[5] This variant has not been reported previously from India.[3] One of the most frequently reported variants from Asia-pacific- c.1935C>A[5] was absent in our group.

Despite advances in investigations, substantial diagnostic delays still prevailed. We noted a mean diagnostic delay of about 6 years (1-14 years) in our study which has not reduced over this long study period. This fact coupled with the paucity of data on LOPD from India[3,6], points to lack of awareness. Increasing awareness among medical practitioners at various levels of primary, secondary and tertiary care may achieve earlier diagnosis of this modifiable disease.

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Date of Submission: 19 May 2025; Date of Acceptance: 30 May 2025

https://doi.org/10.54029/2025dud

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DISCLOSURES

Conflict of interest: None

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