



A database for screening and registering late onset Pompe disease in Turkey

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Abstract

The aim of this study was to search for the frequency of late onset Pompe disease (LOPD) among patients who had a myopathy with unknown diagnosis registered in the pre-diagnostic part of a novel registry for LOPD within a collaborative study of neurologists working throughout Turkey.

Included in the study were 350 patients older than 18 years who have a myopathic syndrome without a proven diagnosis by serum creatine kinase (CK) levels, electrodiagnostic studies, and/or muscle pathology, and/or genetic tests for myopathies other than LOPD. Acid alpha glucosidase (GAA) in dried blood spot was measured in each patient at two different university laboratories. LOPD was confirmed by mutation analysis in patients with decreased GAA levels from either both or one of the laboratories. Pre-diagnostic data, recorded by 45 investigators from 32 centers on 350 patients revealed low GAA levels in a total of 21 patients; from both laboratories in 6 and from either one of the laboratories in 15. Among them, genetic testing proved LOPD in 3 of 6 patients and 1 of 15 patients with decreased GAA levels from both or one of the laboratories respectively. Registry was transferred to Turkish Neurological Association after completion of the study for possible future use and development. Our collaborative study enabled collection of a considerable amount of data on the registry in a short time. GAA levels by dried blood spot even from two different laboratories in the same patient may not prove LOPD. LOPD seemed to be rarer in Turkey than in Europe.

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1. Introduction

Pompe disease is an autosomal recessively inherited rare genetic disorder caused by mutations in the gene responsible for the production of the enzyme acid alpha glucosidase (GAA) [1]. The defective activity or complete elimination of GAA in lysosomes results in massive accumulation of lysosomal glycogen in skeletal muscle in all forms of the disease. The classical or infantile-onset form is characterized by massive cardiomyopathy in addition to the skeletal muscle involvement [2].

Late onset Pompe disease (LOPD) is a very slowly progressive disorder, presenting mainly with skeletal muscle involvement. Respiratory problems develop late in the course. The combination of limb girdle muscle weakness (LGMW) with respiratory distress is a red flag for LOPD. However, it has been reported that the time lapse between the onset of symptoms and establishment of diagnosis in LOPD is quite delayed [3,4]. This is probably due to the insidious onset of an ordinary limb girdle weakness with unexceptional features followed by the insidious onset of respiratory insufficiency, which might be tolerated by the patient for many years.

As a result, seeking medical attention itself may be delayed. On the other hand, lack of awareness and recognition of the disease among medical professionals is another factor. However, the availability of enzyme replacement therapy (ERT) urges now early diagnosis of LOPD as enzyme levels in dried blood spots (DBS) enable also simple screening.

The two well-known international databases for Pompe disease are the Pompe Survey which was established in 2002 in collaboration with International Pompe Association and Erasmus Medical Center, and the Pompe Registry which was created in 2004 by Genzyme, both before ERT was available on the market [3,5]. The Pompe Registry adjusted for the classical form, covered Pompe patients with all forms and the classical form being the most severe form received ERT first. The Pompe Survey has been the major source for non-classical Pompe patients [4]. In 2004 French Registry was created to follow-up French adult Pompe patients [6]. All these registries gathered vast amount of information about features and prognosis of Pompe disease up to date and are currently ongoing.

Most of the prevalence or screening studies are from Western countries. Turkey is a passage between eastern and western populations with high rates of consanguineous marriages (21.1%) [7]. Incidence rates of LOPD in Turkey could differ from Western countries.

From this point of view, we planned to establish a national LOPD registry to collect and share data on LOPD. This registry could also be extended to a pre-diagnostic field, in which LOPD patients could be selected from a pre-determined set of myopathic syndromes without proven diagnosis. The paucity of neuromuscular expert centers in our country prompted the need to connect with general neurologists, both in the urban and rural areas, whose primary interests are not neuromuscular diseases. Such a connection should raise consciousness in neuromuscular diseases, particularly in LOPD and should enable inclusion of the patients from extensive areas.

The aim of this study was to evaluate the findings of the pre-diagnostic group screened for LOPD after setting a registry adjusted for LOPD via a collaborative study of neurologists working throughout Turkey.

2. Materials and methods

The study was conducted in accordance with general clinical practice and ethical principles deriving from the Declaration of Helsinki and from the regulations for observational studies. Ethical approvals were obtained from ethical committees, the primary approval from the Istanbul University, Ethics Committee and the secondary approval from the Affiliated Ethics Committee of Turkish Ministry of Health with the date and number 2012/365–1191. In addition, the legal and comprehensive consent from the Ministry of Health was obtained.

Written informed consents were obtained from all patients prior to any procedure.

Inclusion criteria for the patients were to live in any region of Turkey, to be older than 18 years and to have a myopathic syndrome without a proven diagnosis. The term “patients with myopathic syndrome without a proven diagnosis” defined patients, who had a myopathy confirmed by electrodiagnostic studies and/or serum creatine kinase (CK) levels and were evaluated for final diagnoses by muscle biopsy, and/or genetic tests for myopathies other than LOPD (Table 1). Exclusion criteria for the patients were to be at age under 18 years at the time of registration, to have any systemic metabolic disease likely to cause myopathies or respiratory insufficiency.

Initially, the study invitation addressed the member neurologists of Neuromuscular Research Group of the Turkish Neurological Association. This was the first circle as these neurologists were not from the expert centers but had enough interest in neuromuscular diseases. Then the invitation to join the study group was extended to other neurologists who rarely see neuromuscular patients from all regions of the country. At the end of the announcement and application procedures, neurologists from 32 centers set up the study group. Two consensus meetings with the whole study group were organized: 1 – To train and accord common practice of the neuromuscular examination for general neurologists who rarely examine neuromuscular patients. For educational purposes a live training meeting was held and

Table 1
Myopathic syndromes to be included in the study.

-
- Extremity proximal + axial + respiratory weakness
 - Extremity proximal weakness + ptosis*
 - Extremity proximal weakness + tongue weakness*
 - Extremity proximal weakness without pseudohypertrophy
 - Undefined proximal weakness
 - Paraspinal weakness
 - Rigid spine
 - Asymptomatic hypercreatininemia
 - Undiagnosed respiratory distress (Particularly orthopnea)
 - Pompe disease within the family
 - Facioscapulohumeral Dystrophy (FSHD) phenotype (in sporadic or recessive cases)
-

* Provided that Myasthenia Gravis is excluded.

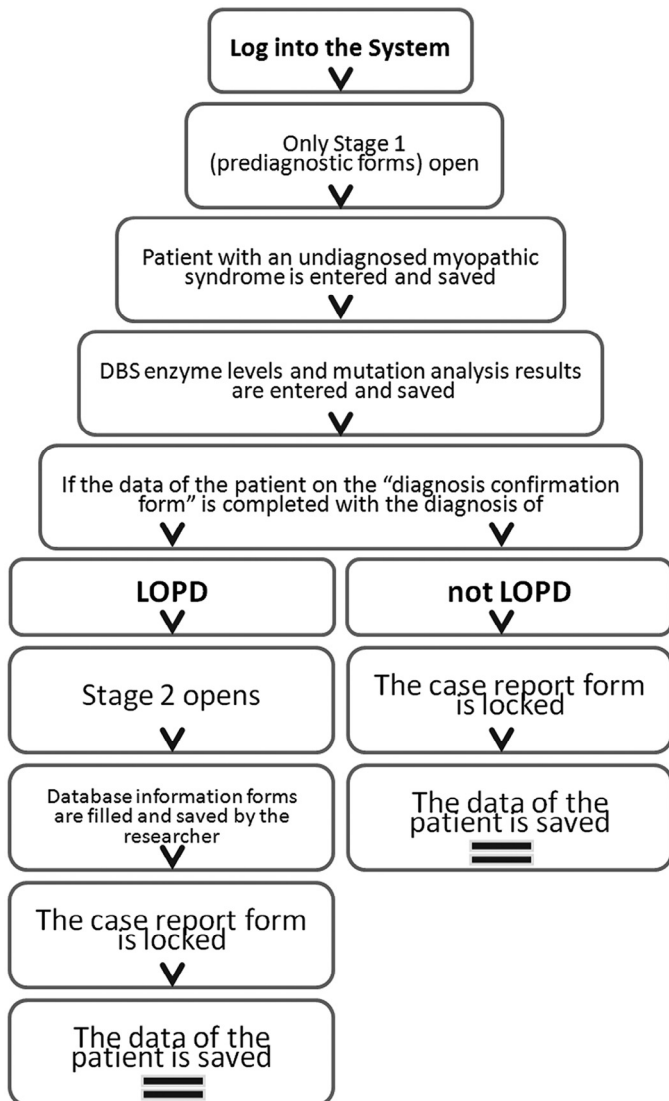


Fig. 1. The sequences of registering patients in pre-diagnostic part of the registry. LOPD: Late onset Pompe disease.

also video embedding into the registry was made to reach a standard evaluation of muscle diseases. 2 – To discuss the questionnaire and the content of the registry. Additional several meetings accomplished consensus on the registry.

Finally, consensus was reached and the registry was based on three separate stages:

Stage 1 was the pre-diagnostic part, prepared for patients selected to screen for LOPD among patients with myopathy but without a proven diagnosis. This part contained three forms, namely the *pre-diagnostic clinical findings form*, the *pre-diagnostic enzyme determination form* and the *diagnostic verification form*, to be completed (Fig. 1).

The *pre-diagnostic clinical findings form* contained clinical pre-determined inclusion criteria for patients who qualified to have a screening test to measure GAA activity. In this list, all the reported features of LOPD were included, regardless of being rare or frequent (Table 1). Both the pre-determined myopathic syndromes to be included and the video recordings

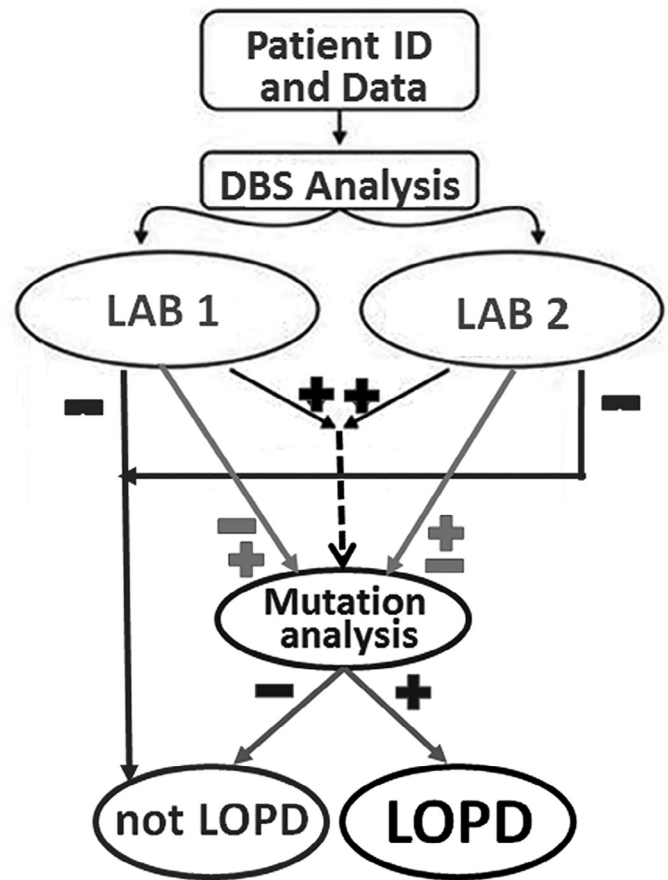


Fig. 2. The algorithm for the diagnosis of LOPD in the pre-diagnostic part of the registry. ID: Identification number; DBS: Enzyme levels in dried blood spots. Lab 1: Laboratory of the Ege University Hospital İzmir. Lab 2: Laboratory of the Hamburg University. LOPD: Late onset Pompe disease.

on how to examine specific muscle groups were prepared and embedded in the corresponding sites of the registry for assistance.

The *pre-diagnostic enzyme determination form* was uploaded after measuring GAA in DBS (Fig. 1). Acid alpha glucosidase in DBS was measured at two different university laboratories (Izmir, Turkey and Hamburg, Germany). LOPD was excluded if the GAA enzyme levels were within normal limits in both laboratories (Fig. 2). Further data entry for these excluded patients was prevented by locking the system for that patient at this stage.

If both or one of the DBS enzyme levels was low, mutation analysis was performed. The diagnostic verification form was reserved for the results of the mutation analysis to demonstrate the final decision for the diagnosis, namely LOPD or non-LOPD (Fig. 1 and 2). If the patients did not qualify for a diagnosis of LOPD, their data entries were also locked but these patients were reserved for final statistical evaluation (Fig. 2).

Stage 2 and **stage 3** were reserved for patients who had a definite diagnosis of LOPD after DBS and mutation analysis, for detailed initial and follow-up examinations.

The database was opened for a trial period of 2 months to see if there was any problem to be solved. It was accessible only for

members of the group on the web site www.pompevt.com where “pompevt” represented the first letters of “National Database for Pompe Disease” in Turkish. Each member signed in with a personal password and could see only patients recorded by him- or herself while the Principal Investigator had access to see the information on all registered patients. A formula based on the national identity number in association with the first letters of forename and family name was set up to identify each patient. Recurrent data input of the same patient was avoided by this formula while the system did not accept recurrent input of the patient with the same identity number (ID) after the first record on the database (view demo on Tnd-LOPD.org). This precaution was necessary because it would be possible that some patients with chronic and not curable diseases visit more than one hospital and neurologist had not yet informed the last one about the previous visits.

Finally, the study started in December 2013, collecting data of minimum 168 patients who underwent screening tests for the pre-diagnostic part until June 2014. As this number was reached long before the deadline, a second approval of the ethical committee was obtained for a total of 450 patients and for a total of 6-month period. An independent analyst checked each input of the newly recorded patients and then locked the appropriate patient entry after the DBS and DNA results were entered.

After completion of the study period, the database was transferred from the research group to Turkish Neurological Association for further use and development. In order to open the database to international discussion, an English version is prepared and named as Tnd-LOPD, which refers to Turkish National Database for LOPD (go to URL for demo: Tnd-LOPD.org).

For statistical analysis of the data of patients entered in stage 1, chi-square tests in IBM SPSS statistics 23 was used.

3. Results

Forty-five investigators from 32 centers entered data of 413 patients in the pre-diagnostic part (stage 1) of the registry. Sixty-three of these 413 patients were excluded because GAA enzyme levels were missing at the end of the study.

The *pre-diagnostic clinical findings form* was completed for a total of 350 patients. There were 178 males and 172 females aged between 19 and 80 years (41.11 ± 13.28). The maximum duration of the complaints was 48 years whereas the minimum duration was 0 years (mean \pm SD: 13.4 ± 11.84 years). A “duration of zero years” referred to 32 patients with asymptomatic high CK levels. Unexplained proximal weakness and proximal weakness without pseudohypertrophy were the most frequent findings whereas rigid spine, paraspinal weakness and unexplained respiratory distress were the least frequent syndromes entered in the *pre-diagnostic findings form* (51,1%; 26,6%; 1,7%; 1,4%; and 2,9% respectively).

Results of DBS measurements which were recorded in the *pre-diagnostic enzyme determination forms* are demonstrated in [Table 2](#). Pre-diagnostic data, revealed low GAA levels in a total of 21 patients (6%), from both laboratories in 6 and from either one of the laboratories in 15. Among them, genetic testing

Table 2

Comparison of the DBS results obtained from 2 laboratories.

		GAA* in Hamburg, Mainz University		
		Normal	Decreased	Total
GAA* in İzmir,	Normal	329	4	333
Ege University	Decreased	11	6	17
Total		340	10	350

* Acid alpha glucosidase.

Table 3

Pre-diagnostic clinical findings in 350 patients.

Clinical Syndromes in 350 patients	In LOPD	In non-LOPD	In total group
Weakness in prox.* ax. and resp† m.‡	0	29	29
Weakness in prox. m. and ptosis	0	15	15
Weakness in prox. m. and in tongue	0	9	9
Weakness in prox. m. without psdht§	3	90	93
Unexplained proximal weakness	1	178	179
Paraspinal weakness	0	5	5
Rigid spine	0	6	6
Asymptomatic high levels of CK¶	0	32	32
Unexplained respiratory distress	0	10	10
LOPD# in family history	1††	10	11
FSHD** phenotype (recessive or sporadic)	0	19	19

* Proximal.

† Respiratory.

‡ Muscles.

§ Pseudohypertrophy.

¶ Creatin kinases.

Late onset Pompe disease.

** Facioscapulohumeral muscular dystrophy.

†† One of the 3 patients with proximal weakness without pseudohypertrophy.

proved LOPD in 3 of 6 patients and 1 of 15 patients with decreased GAA levels from both or one of the laboratories, respectively.

In short, among 350 patients of pre-diagnostic group, LOPD was verified in a total of 4 patients, 2 females and 2 males (1.14%) by means of mutation analysis, although low enzyme levels in DBS measurements were detected in 21 (6%). Of the 4 LOPD patients, neurological examinations revealed proximal weakness without pseudohypertrophy in 3, 1 of who had family history of LOPD. Unexplained proximal weakness was detected in a last one patient. None of the 32 patients with “asymptomatic CK elevation” proved to have LOPD by mutation analysis, though 3 of them (9.4%), 2 from Hamburg and 1 from Izmir Laboratories, had low enzyme levels in DBS measurements.

[Table 3](#) compares the myopathic syndromes of the verified LOPD patients with non-LOPD patients in the pre-diagnostic group. The ratio of LOPD patients and non-LOPD patients did not reveal a significant difference in any myopathic syndrome ($p > 0.05$). Also, their ages [$52,7 \pm 17,9$ (39–73) in LOPD and $41,67 \pm 13,5$ (20–80) in non-LOPD] and the durations of their complaints [$12 \pm 9,2$ (2–20) and $13,5 + 12$ (0–48) respectively] did not differ significantly ($p > 0.05$).

4. Discussion

Many groups presented the genotypic and phenotypic features of their LOPD patients. Regarding the registries, to our

knowledge, French registry is the only national registry adjusted for LOPD [6].

Our national registry differs from those previously presented, in that it consists of three stages in which the first stage was dedicated to put data of patients searched for LOPD among patients with myopathy who had no proven diagnoses. By doing this we were able to keep data of patients with myopathic syndromes without a definite diagnosis as well as proven LOPD patients within the same registry. Collected data from 413 patients by 45 investigators during a 6-month period indicated that one of the purposes of the registry, defined as “to evoke interest and restore knowledge on neuromuscular disorders with special attention to LOPD” was fulfilled. As the registry was transferred to the Turkish Neurological Society, it now can be used for further studies and can be further developed with discussions.

There are many reports on seeking LOPD among patients with limb girdle muscle weakness (LGMW) with or without respiratory distress and/or pauci-symptomatic CK elevation [8–18]. Some of these studies took histopathological features into consideration as well [17]. All studies, performed at expert centers showed that the incidence of LOPD range from 1.6 to 5.9, among patients with undetermined myopathies and/or high CK levels [8–19].

In this study, although our inclusion criteria comprised all the described features of LOPD, the incidence of LOPD was found to be 1.14%, most with “proximal weakness without pseudohypertrophy”. This ratio seems lower than those found in other series [9–19]. It also seemed obscure in our study that, although 9.4% of them had low enzyme levels in DBS measurements, none of the patients with “asymptomatic CK elevation” proved to have LOPD in contrast to all the previous reports (10, 14, and 16).

A striking difference between our and Preisler’s study exists in the frequent respiratory muscle involvement [11]. Although special attention was given, our patients may not have been evaluated enough for respiratory problems and more attention should be given for the recognition of this aspect in daily practice.

If we look at DBS results, the ratio of the patients with low enzyme levels from either both or one of the laboratories is quite compatible with other reports of proven LOPD patients (8–19). As mutation analysis is the gold standard to diagnose LOPD today, patients with decreased enzyme levels from both laboratories or even from one laboratory underwent mutation analysis. Only 1.14% achieved the diagnosis of LOPD by mutation analysis in contrast to 6% of patients with low enzyme levels on DBS. Our study showed that DBS measurements revealed low enzyme levels at a ratio much higher than the ratio of the LOPD patients proven by mutation analysis. The low enzyme levels could be false positives due to the setting of the cut off for the GAA assay or the difference could be GAA pseudo-deficiency in some of them. To our knowledge, the sensitivity and specificity of GAA levels measured by DBS in LOPD were not compared with mutation analysis results yet and are subject to be evaluated in future studies.

Our results might implicate an explanation for the low ratio of proven LOPD patients.

Turkey is genetically a passage between eastern and western populations and harvests different genetic backgrounds [20]. Although the rate of consanguineous marriages is high in our country, LOPD was not found more frequent in Turkey than in European countries. The question of diversity of mutations for LOPD in Turkey is again another subject for future research.

In conclusion, our model of registry and the evaluation of the pre-diagnostic findings shed light on some aspects of identification of LOPD not sufficiently discussed yet. Our collaborative study enabled collection of the considerable amount of data on the registry in a short time. LOPD seemed to be rarer in Turkey than in Europe.

Turkish Study Group for Late Onset Pompe Disease

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Appendix: Supplementary material

Supplementary data to this article can be found online at Tnd-LOPD.org as demo.

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