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Original Article

Clinical and genetic spectrums of pompe disease in Duhok city, Kurdistan region, Iraq

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Abstract

Pompe disease which is glycogen storage disease type II, is an autosomal recessive lysosomal storage disorder where GAA gene mutations cause deficiency of acid alpha-glucosidase leading to deposition of glycogen in various tissues. Chromosome 17q25.2–25.3 is the location of GAA gene. This study aims to collect information on the Pompe disease symptoms' severity and genotypes of 18 children who represented all infant patients with Pompe disease until March 1st, 2024. For diagnosis tandem mass spectrometry and genetic study were used. Muscle strength was assessed by hand-held dynamometry. Cardiac assessment was by echocardiography and electrocardiography. The feeding and swallowing difficulties in the patients were addressed. Statistical analysis was used P<0.05 was considered significant. Fifty percent had normal mental development, 27.8% had delayed mile stones 55.6% had weakness of extremities, 50% had heart problems in the first month,38.8% had respiratory problems in the first month and 12(66.6%) had feeding difficulties. The level of the enzyme alpha-1,4 Glucosidase level was Zero in two patients 66.7% and was 0.1µmol/L/h in 33.3% of the alive patients while it was 0.1 µmol/L/h in 73.3% and 0.2 µmol/L/h in 13.3% of the dead with a significant correlation. The genetic mutations were c. [258dupC]; [258dup] in 6 (33.3%) of the patients, c.258dup in 3(16.6%) and c.2237G>A in 11.1% of all the patients. Childhood Pompe disease course varies widely. It is important to consider Pompe disease in the differential diagnosis of patients with unexplained fatigue and weakness and cardiorespiratory involvement.

Keywords: Pompe, Mutation, Infancy, Alpha-1,4 Glucosidase, Ventilator, Weakness.

1. Introduction

Pompe disease which is also called glycogen storage disease type II, is a lysosomal storage disorder inherited as autosomal recessive. GAA gene mutations cause deficiency of the lysosomal enzyme acid alpha-glucosidase leading to deposition of glycogen in various tissues. Pompe disease is classified as infantile-onset and late-onset forms depending on the age of onset, severity of involvement of organ and progression rate. The classic infantile-onset Pompe disease (IOPD) presents before the age of one year with rapid hypotonia, progressive cardiomyopathy, feeding difficulties and respiratory insufficiency. Without treatment, this causes death before the second year of life from cardiorespiratory failure [1]. They present shortly after birth with generalized and severe muscle weakness and hypertrophic cardiomyopathy and do not reach major gross motor milestones like walking and may even die within their first year of life. Pompe disease is considered a continuous spectrum of closely related phenotypes with the classic infantile form at the most severe end of the spectrum [2].

Chromosome 17q25.2–25.3 is the location of GAA gene. It contains 20 exons and spans approximately 20 kb. Till now, 648 disease variants have been identified and have been listed in the database of Pompe disease variants (http://www.pompevariantdatabase.nl/ updated in 2020) [3]. All mutation types have been described, the most frequent of which are missense mutations. Some mutations are more frequently found in certain geographical regions, for example, the intronic c.-32-13T>G mutation in individuals of European descent, the c.1935C>A p.(D645E) mutation in the South of China and c.2662G>T p.(E888*) mutation in the North of China [4]. Studies have described more than 300 different mutations responsible for Pompe disease [5,6], without finding strict correlations between genotype and phenotype [7]. Noticeable variations in disease severity have been observed within families; a study by Wens et al. [8] found that the presenting symptoms were different in siblings in 36% of families.

Enzyme replacement therapy (ERT) with recombinant alglucosidase alpha (rhGAA) has noticeably improved outcomes for IOPD patients like reversing cardiomyopa-

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thy, improving motor function and increasing survival [1]. Early treatment with ERT before the onset of irreversible muscle damage is associated with better outcomes [9]. However, response to ERT is variable, with suboptimal outcomes in some patients even when treatment is started early [10,11]. Cross-reactive immunological material (CRIM) negative patients cannot synthesize native GAA enzymes and develop high sustained titers of rhGAA antibodies [12]. They respond poorly to treatment and require immunomodulation before initiating ERT [13]. CRIM status can be predicted for most patients depending on their genotype [14].

To obtain a good knowledge of the presentation of Pompe disease in children and to specify their clinical characteristics, this observational study was set up to collect information on the Pompe disease symptoms, the severity and distribution of muscle weakness, lung function, physical limitations, cardiac structure and function and genotypes of 18 children diagnosed with Pompe disease.

2. Materials and methods

2.1. Study design

This observational study included all infant patients diagnosed and treated at the Rare Disease Center at Heevi Pediatric Teaching in Duhok until March 1st, 2024. Ethical approval for the study was obtained from the Health Ethics Committee of the local directorate of health.

2.1. Diagnostic methods

For diagnosis, tandem mass spectrometry using dried blood spots was employed to determine enzyme levels (alpha-1,4 Glucosidase activity) and genetic studies (DNA extraction from dried blood spots; PCR amplification and sequencing of all coding exons and flanking intronic regions) were conducted by ARCHIMED Life Laboratories, Vienna, Austria.

2.2. Laboratory tests

The patients were sent for blood tests including creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH).

2.3. Neurological and muscle assessments

Neurological examinations were performed for all patients. Muscle strength was assessed using hand-held dynamometry for various muscle groups including neck flexors, elbow flexors, wrist extensors, shoulder abductors, hip abductors, hip flexors, knee extensors, knee flexors and foot dorsal flexors

2.4. Cardiac assessment

Cardiac evaluations included Conventional Doppler ultrasound, 2D M-mode echocardiography and Standard 12-lead electrocardiograms analyzed by a pediatric cardiologist

2.5. Data management and statistical analysis

Data were entered into a Microsoft Excel sheet and analyzed using SPSS version 23. The following statistical analyses were performed.

Descriptive statistics were performed to calculate the mean and standard deviations, along with the frequency (%) of the data. Continuous variables were presented as mean ± SD, accompanied by minimum and maximum values. Categorical variables were reported as frequency (%). For statistical analysis, Chi-squared (χ^2) and Fisher's Exact Tests were conducted, with a p-value of ≤0.05 considered statistically significant.

3. Results

3.1. Distribution by neurologic findings

As shown in Table 1, Mental development was normal in 50% and could not be assessed in 50% of patients. Major mile stones were delayed in 27.8% and even not achieved in 72.2% of patients. The most frequent age of onset of hypotonia was the first month of life in 44.4% of patients. Neck muscle involvement started in the first month in 44.4% of patients while in 22.2% the neck muscles were not involved. Frog leg posture was present in 6 (33.3%) patients with the most frequent age of onset being 2 months. Weakness of arms and legs was in 55.6% of patients while legs only were involved in 38.9%. Pseudohypertrophy was present in 11.1% of patients and muscle atrophy was also detected in 11.1% of patients. None of the patients had ptosis or contracture.

3.2. Distribution by cardiorespiratory findings

As shown in Table 2, The age of onset of heart problems was the first month in 50% of patients while in 33.3% it was in the second month of life. Respiratory difficulties and respiratory infections were detected in the first month of life in 38.8% of cases followed by 22.2% in the third month of life. Oxygen dependence was observed in 12 (66.6%) with the most frequent age of onset of oxygen dependence being 3 months in 22.2%. Ventilator dependence was found in 5 (27.7%).

3.3. Characteristics of different genetic mutations with GIT findings

Feeding difficulties were observed in 12(66.6%) patients and the most frequent age of observing these difficulties was the first month 27.8%. Swallowing problems were also observed in 12(66.6%) of patients with the most frequent age of onset being 2 and 3 months. Large tongue was observed in 6 (33.3%) of patients. Liver problems were present in 5 (27.7%) patients most frequently in the first month of life. Seven (38.8%) patient showed digestive problems with the most common age of their observation being nine months (11.1%) as shown in Table 3.

3.4. Survival and association with different variables

Three of the patients (16.6%) were still alive at the time of the study. Two of the survivors had the mutation c.258dup and one had the mutation c.1210G>A while the most frequent mutation among deceased patients was c.[258dupC];[258dupC] followed by c.2237G>A. The association was not statistically significant. Consanguinity of parents was present in all the alive patients 100% while 80% of the dead had consanguinity between parents without significant relation. Male: female ratio was 2:1 among the alive while it was 0.87:1 among the dead patients with no significant association. The level of the enzyme alpha-1,4 Glucosidase level was Zero in two patients 66.7% and was 0.1μmol/L/h in 33.3% of the alive patients while it was 0.1 μmol/L/h in 73.3% and 0.2 μmol/L/h in 13.3% of the dead with a significant correlation. Birth order was the second, third and fourth in each one of the alive while

Table 1. Characteristics of different genetic mutations with clinical neurological findings.

Neurological Findings	c. [258dupC]; [258dup] N=6 (%)	c.258dup N=3 (%)	c.2237G>A N=2 (%)	Others N=7 (%)	Total N=18 (%)
Mental Development					
Normal	3 (50.0%)	0 (0.0%)	1 (50.0%)	5 (71.4%)	9 (50.0%)
Can't be assessed	3 (50.0%)	3 (100.0%)	1 (50.0%)	2 (28.6%)	9 (50.0%)
Major Milestones Assessment / Months					
Delayed	2 (33.3%)	0 (0.0%)	1 (50.0%)	2 (28.6%)	5 (27.8%)
Not achieved	4 (66.7%)	3 (100.0%)	1 (50.0%)	5 (71.4%)	13 (72.2%)
Age of Hypotonia / Months					
1	1 (16.7%)	2 (66.7%)	1 (50.0%)	4 (57.1%)	8 (44.4%)
2	2 (33.3%)	0 (0.0%)	0 (0.0%)	2 (28.6%)	4 (22.2%)
3	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
4	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (5.6%)
6	2 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
No	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (5.6%)
Age of Neck Involvement / Months					
1	2 (33.3%)	1 (33.3%)	1 (50.0%)	4 (57.1%)	8 (44.4%)
3	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
6	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
7	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (5.6%)
No	2 (33.3%)	0 (0.0%)	0 (0.0%)	2 (28.6%)	4 (22.2%)
Not achieved	1 (16.7%)	1 (33.3%)	0 (0.0%)	1 (14.3%)	3 (16.7%)
Age of Frog Leg Posture / Months					
2	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (5.6%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)	2 (11.1%)
5	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
6	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (5.6%)
8	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (5.6%)
No	5 (83.3%)	3 (100.0%)	1 (50.0%)	3 (42.9%)	12 (66.7%)
Location of Weakness					
Arms	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
Legs	1 (16.7%)	2 (66.7%)	1 (50.0%)	3 (42.9%)	7 (38.9%)
Both are the same	4 (66.7%)	1 (33.3%)	1 (50.0%)	4 (57.1%)	10 (55.6%)
Presence of Ptosis					
No	6 (100.0%)	3 (100.0%)	2 (100.0%)	7 (100.0%)	18 (100.0%)
Presence of Pseudohypertrophy					
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)	2 (11.1%)
No	6 (100.0%)	3 (100.0%)	2 (100.0%)	5 (71.4%)	16 (88.9%)
Presence of Contractures					
No	6 (100.0%)	3 (100.0%)	2 (100.0%)	7 (100.0%)	18 (100.0%)
Muscle Atrophy					
No	6 (100.0%)	3 (100.0%)	2 (100.0%)	5 (71.4%)	16 (88.9%)
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)	2 (11.1%)

Table 2. Characteristics of different genetic mutations with cardiorespiratory findings.

Category	c.[258dupC];[258dup (N=6)	c.258dup (N=3)	c.2237G>A (N=2)	Others (N=7)
Age of Observed Heart Problems/Months				
1	4 (66.7%)	0 (0.0%)	2 (100.0%)	3 (42.9%)
2	2 (33.3%)	0 (0.0%)	0 (0.0%)	4 (57.1%)
4	0 (0.0%)	3 (100.0%)	0 (0.0%)	0 (0.0%)
Age of Observed Respiratory Difficulties/Months				
1	2 (33.3%)	1 (33.3%)	1 (50.0%)	3 (42.9%)
1.5	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
2	0 (0.0%)	0 (0.0%)	1 (50.0%)	1 (14.3%)
3	1 (16.7%)	2 (66.7%)	0 (0.0%)	1 (14.3%)
4	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
6	2 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Age of Observed Respiratory Infections/Months				
1	2 (33.3%)	2 (66.7%)	1 (50.0%)	2 (28.6%)
1.5	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
2	0 (0.0%)	0 (0.0%)	1 (50.0%)	1 (14.3%)
3	1 (16.7%)	1 (33.3%)	0 (0.0%)	1 (14.3%)
6	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
No	2 (33.3%)	0 (0.0%)	0 (0.0%)	2 (28.6%)
Age of Observed Oxygen Dependence/Months				
1	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)
2	0 (0.0%)	1 (33.3%)	0 (0.0%)	1 (14.3%)
3	2 (33.3%)	1 (33.3%)	1 (50.0%)	0 (0.0%)
4	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
6	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
8	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
24	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
No	2 (33.3%)	1 (33.3%)	0 (0.0%)	3 (42.9%)
Age of Observed Ventilator Dependence/Months				
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
3	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)
7	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
24	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
No	5 (83.3%)	2 (66.7%)	2 (100.0%)	4 (57.1%)

Table 3. Characteristics of different genetic mutations with GIT findings.

Categories	c. [258dupC];[258dup] N=6 (%)	c.258dup N=3 (%)	c.2237G>A N=2 (%)	Others N=7 (%)	Total N=18 (%)
Age of Observed Feeding Problems (Months)					
1	1 (16.7%)	0 (0.0%)	1 (50.0%)	3 (42.9%)	5 (27.8%)
2	0 (0.0%)	1 (33.3%)	0 (0.0%)	1 (14.3%)	2 (11.1%)
3	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	2 (11.1%)
4	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
6	2 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
No	2 (33.3%)	1 (33.3%)	1 (50.0%)	2 (28.6%)	6 (33.3%)
Age of Observed Swallowing Problems (Months)					
1	1 (16.7%)	0 (0.0%)	1 (50.0%)	3 (42.9%)	5 (27.8%)
2	0 (0.0%)	1 (33.3%)	0 (0.0%)	1 (14.3%)	2 (11.1%)
3	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	2 (11.1%)
4	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
5	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
6	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
No	2 (33.3%)	1 (33.3%)	1 (50.0%)	2 (28.6%)	6 (33.3%)
Presence of Observed Large Tongue					
Yes	3 (50.0%)	0 (0.0%)	1 (50.0%)	2 (28.6%)	6 (33.3%)
No	3 (50.0%)	3 (100.0%)	1 (50.0%)	5 (71.4%)	12 (66.7%)
Age of Observed Liver Problems (Months)					
1	0 (0.0%)	0 (0.0%)	1 (50.0%)	1 (14.3%)	2 (11.1%)
6	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
10	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
24	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
No	3 (50.0%)	3 (100.0%)	1 (50.0%)	6 (85.7%)	13 (72.2%)
Age of Observed Digestive Problems (Months)					
1	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (5.6%)
4	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
6	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (5.6%)
9	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)	2 (11.1%)
12	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (5.6%)
No	4 (66.7%)	3 (100.0%)	1 (50.0%)	3 (42.9%)	11 (61.1%)

the most frequent birth order of the dead was the second in 46.7% of the dead with no significant association. None of the live patients had another affected sibling while 60% of the dead had an affected sibling and 53.3% had a history of a dead affected sibling without a significant association. The cause of death was chest infection 26.7% and heart failure 26.7% and unknown in 33.3% as shown in Table 4.

3.5. Molecular diagnosis

The genetic mutations were c. [258dupC];[258dup] in 6 (33.3%) of the patients, c.258dup in 3(16.6%) and c.2237G>A in 11.1% of all the patients. Other less frequent mutations were c. [2237G>AJ;[2237G>A], c. [2608C>T]:[2608C>T], c.1210G>A and c.896T>C.

4. Discussion

There is a dearth of information on the clinical presentation of children with Pompe disease, we evaluated the molecular and clinical characteristics of 18 patients. Our findings show that Pompe disease can cause a noticeable burden on childhood and help us understand that Pompe disease has a broad spectrum of clinical phenotypes.

In this study, the onset of hypotonia was most frequently in the first month of life with significant delay of the major motor milestones. This onset age is earlier than that reported in another study, where the age of onset was 2.6 years, and in a separate study where the mean age was 2.5 years [15]. This denotes that the high index of suspicion is greatly helpful in reaching an early diagnosis. The neck muscle involvement was in 61.1% of cases which is lower than another study where it was 75%[main] and another study where it was 70.5% 16. The upper and lower limb involvement was in all of the patients in line with another study 16. Muscle atrophy was present in 11% of patients which is lower than another study where it was 35% [2] which denotes younger age at diagnosis in our study [1].

Heart problems were detected in all the patients with the most frequent age at diagnosis being the first month of life in line with a Malaysian study [1]. This is higher than a British study which showed 79% of Pompe disease patients had heart involvement 15 and a Dutch study where it was only 19.3% [2].

Table 4. Characteristics of live children with different variables.

Genetic	Alive N=3 (%)	Dead N=15 (%)	P value
c. [2237G>AJ; [2237G>A]	0 (0.0%)	1 (6.7%)	
c. [258dupC];[258dupC]	0 (0.0%)	6 (40.0%)	
c. [2608C>T]: [2608C>T]	0 (0.0%)	1 (6.7%)	
c. [1848C>A]: [1848C>A]	0 (0.0%)	1 (6.7%)	
c. [259dupC]: [259dupC]	0 (0.0%)	1 (6.7%)	
c. 1210G>A	1 (33.3%)	0 (0.0%)	0.154
c. 2237G>A	0 (0.0%)	2 (13.3%)	
c. 258dup	2 (66.7%)	1 (6.7%)	
c. 258dupC	0 (0.0%)	1 (6.7%)	
c. 896T>C	0 (0.0%)	1 (6.7%)	
Consanguinity			
Yes	3 (100.0%)	12 (80.0%)	
No	0 (0.0%)	3 (20.0%)	0.396
Sex			
Male	2 (66.7%)	7 (46.7%)	
Female	1 (33.3%)	8 (53.3%)	0.527
Enzyme Level			
0.2	0 (0.0%)	2 (13.3%)	
0.15	0 (0.0%)	1 (6.7%)	
0.1	1 (33.3%)	11 (73.3%)	0.022
0.06	0 (0.0%)	1 (6.7%)	
0	2 (66.7%)	0 (0.0%)	
Birth Order			
1	0 (0.0%)	2 (13.3%)	
2	1 (33.3%)	7 (46.7%)	
3	1 (33.3%)	1 (6.7%)	
4	1 (33.3%)	1 (6.7%)	0.609
5	0 (0.0%)	2 (13.3%)	
6	0 (0.0%)	1 (6.7%)	
7	0 (0.0%)	1 (6.7%)	
Another Affected Sibling			
Yes	0 (0.0%)	9 (60.0%)	
No	3 (100.0%)	6 (40.0%)	0.058
Sibling Death History			
Yes	0 (0.0%)	8 (53.3%)	
No	3 (100.0%)	7 (46.7%)	0.09
Cause of Death			
Alive	3 (100.0%)	0 (0.0%)	
Chest infection	0 (0.0%)	4 (26.7%)	
Heart failure	0 (0.0%)	4 (26.7%)	0.003
Not known	0 (0.0%)	5 (33.3%)	
Resp. Failure	0 (0.0%)	1 (6.7%)	
Stroke	0 (0.0%)	1 (6.7%)	

Respiratory difficulties were detected in 61.1% of patients with the most frequent onset in the first month of life which is even higher than a study that found 53% of children with Pompe disease having respiratory difficulties [17] and lower than another study found 70% of patients developing significant respiratory difficulties [15]. However, 27.7% of the patients were ventilator-dependent which is higher than a study that found 17% of patients were ventilator-dependent but significantly lower than another study where it was 48% 2 and 94% [1]. This finding stresses the significance of early monitoring of lung volume by means of spirometry in children affected by Pompe disease [17].

Feeding and swallowing problems were detected in 66.6% of patients with the most frequent onset at the first month of life which is in line with another study that found 69.5% of children with Pompe disease had gastroesophageal reflux and swallowing difficulties [10] and lower than another study where it was 76% [1].

The sex distribution of the patients was equal between

males and females 1:1. This is different from other studies that revealed that childhood-onset Pompe disease was more common in males [2,17,18].

The genetic mutations of the patients were most frequently c. [258dupC];[258dup] while in a Dutch study, the most frequent was c.-32– 13T > G/'null' genotype [2] another study showed the most frequent gene was c.1935C>A p.(D645E) [1]. A Thai study showed four novel variants: c.876C > G (p.Tyr292X), c.1226insG (p.Asp409GlyfsX95), c.1538G > A (p.Asp513Gly) and c.1895 T > G (p.Leu632Arg) [19]. A German study as well as a study in the Netherlands showed the mutation c.-32-13T>G as the most frequent one [16,20]. Another Dutch study showed the most frequent mutation as c.510 C>T [15].

Our study had two main limitations. First, since Hevi Pediatric Teaching Hospital serves as a referral centre for Pompe disease, there may be selection bias because the most severely affected patients are referred to our centre. A second limitation is the fact that the study was cross-sectional and all children manifesting significant symptoms of the disease, started to receive enzyme replacement therapy that interfered with the collection of longitudinal follow-up data.

5.Conclusion

In conclusion, our study shows that childhood Pompe disease course varies widely. It is important to consider Pompe disease in the differential diagnosis of patients with unexplained fatigue and weakness of the neck flexors, especially in the first months of life. Cardiorespiratory involvement is a common early presentation in infants with Pompe disease. The most frequent genetic mutations of the patients were c. [258dupC]; [258dup]. Two-thirds of patients with Pompe disease show feeding and swallowing difficulties.

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None

Conflict of interest

The authors declare no conflict of interest.

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