Cardiac disease in children and young adults with various lysosomal storage diseases: Comparison of echocardiographic and ECG changes among clinical groups

Mueller, P ; Attenhofer Jost, C H ; Rohrbach, M ; et al

Abstract: Background: Lysosomal storage disease (LSD) is a rare inherited disease group. Consecutively there are few data on cardiac changes in mucopolysaccharidosis (MPS), Anderson Fabry disease (AFD), and other LSD (oLSD) including Pompe disease (PD) and Danon disease (DD), I-cell disease (ICD) and mucolipidosis III (ML III). Methods: Between 1994 and 2011, we identified 39 patients with LSD: 25 with MPS, 8 with AFD, and 6 with oLSD including PD (1), ML III (2), DD (1), and ICD (2) at our institution fulfilling the inclusion criteria of at least one echocardiogram and ECG. Results: Median age was 11.4 years (range: 2–27), 22 were females (56%). Normal echocardiograms were present in 12 patients (31%): 4 with MPS (16%), 7 AFD (88%), and 1 oLSD (17%). Valvular heart disease was present in 23 patients (59%) occurring more often in MPS (76%) and oLSD (67%) than in AFD (0%) (p < 0.001). The most common ECG abnormality was a short PR interval in 10 of 35 patients (29%) occurring in all LSD groups. Median follow-up was 5.8 (0.2–22.2) years showing diminished 5-year survival compared to an age-matched group. However, no patient died due to a cardiac cause and no cardiovascular intervention was necessary. Conclusion: Echocardiographically detectable cardiovascular involvement in children with LSD is mostly confined to MPS and oLSD. Valve thickening in echo and a short PR interval in the ECG are the most frequent abnormalities. Routine repeat assessment is recommended in LSD. However, significant cardiac disease necessitating cardiac intervention is rare during a short follow-up.

DOI: https://doi.org/10.1016/j.ijchv.2013.10.002

The following work is licensed under a Creative Commons: Attribution-NonCommercial-NoDerivs 3.0 Unported (CC BY-NC-ND 3.0) License.

Originally published at: Mueller, P; Attenhofer Jost, C H; Rohrbach, M; et al (2014). Cardiac disease in children and young adults with various lysosomal storage diseases: Comparison of echocardiographic and ECG changes among clinical groups. International Journal of Cardiology. Heart Vessels, 2:1-7. DOI: https://doi.org/10.1016/j.ijchv.2013.10.002
Cardiac disease in children and young adults with various lysosomal storage diseases: Comparison of echocardiographic and ECG changes among clinical groups

P. Mueller, C.H. Attenhofer Jost, M. Rohrbach, E.R. Valsangiacomo, B. Seifert, C. Balmer, O. Kretschmar, M.R. Baumgartner, R. Weber

1. Introduction

Lysosomal storage disease (LSD) is a heterogeneous group of more than 40 different disorders due to genetic defects in a lysosomal acid hydrolase, causing progressive lysosomal accumulation of substrates specific for each disorder involving multiple organs; the severity of disease depends on residual enzyme activity. LSD shows an accumulation of various glycosaminoglycans, glycoproteins, or glycolipids within the lysosomes of various tissues [1]. LSD can affect the heart and constitute an important distinct and treatable cause of cardiomyopathy in children, accounting for approximately 5% of pediatric cardiomyopathies [2]. The most common LSDs in children are Anderson–Fabry disease (AFD), mucopolysaccharidosis (MPS), Pompe disease (PD), and Danon disease (DD) [3]. In adults, AFD is the most prevalent LSD; cardiac involvement in AFD in adults can mimic hypertrophic cardiomyopathy [4]. In MPS pronounced cardiovascular involvement can be a cause of death apart from upper airway obstruction [5–7]. There are only rare studies comparing cardiac involvement between the various types of LSD. Most of these studies focus on one large group of the disorders such as MPS [7].

The aim of this study was first to describe and compare echocardiographic findings of clinical symptoms and ECG in children with LSD in a single institution, and second to analyze the possible impact of cardiac disease on survival.

2. Methods

2.1. Patients

The echocardiography database of the Children's University Hospital Zurich was searched from January 1994 to April 30, 2011. All patients with a diagnosis of MPS, AFD, mucopolysaccharidosis II and III (ML), Pompe disease (PD), or Danon (DD) disease were reviewed to meet our inclusion criteria of a biochemical or genetic diagnosis of the respective LSD. If the underlying cause of death was attributed to a cardiac event or other complications, the patient was excluded from the study. A total of 40 patients fulfilling the inclusion criteria were included in the analysis.

Methods: Between 1994 and 2011, we identified 39 patients with LSD: 25 with MPS, 8 with AFD, and 6 with oLSD including PD, DD, and ICD (2) at our institution fulfilling the inclusion criteria of at least one echocardiogram and ECG.

Results: Median age was 11.4 years (range: 2–27), 22 were females (56%), Normal echocardiograms were present in 12 patients (31%): 4 with MPS (16%), 7 AFD (88%), and 1 oLSD (17%). Valvular heart disease was present in 23 patients (59%) occurring more often in MPS (76%) and oLSD (67%) than in AFD (0%) (p < 0.001). The most common ECG abnormality was a short PR interval in 10 of 35 patients (29%) occurring in all LSD groups. Median follow-up was 5.8 (0.2–22.2) years showing diminished 5-year survival compared to an age-matched group. However, no patient died due to a cardiac cause and no cardiovascular intervention was necessary.

Conclusion: Echocardiographically detectable cardiovascular involvement in children with LSD is mostly confined to MPS and oLSD. Valve thickening in echo and a short PR interval in the ECG are the most frequent abnormalities. Routine repeat assessment is recommended in LSD. However, significant cardiac disease necessitating cardiac intervention is rare during a short follow-up.

© 2013 Elsevier Ireland Ltd. All rights reserved.

Please cite this article as: Mueller P, et al, Cardiac disease in children and young adults with various lysosomal storage diseases: Comparison of echocardiographic and ECG changes among clinical groups, IJC Heart & Vessels (2013), http://dx.doi.org/10.1016/j.ijchv.2013.10.002
criteria; as one patient refuses any research participation, 39 patients were included in the study. The local ethical committee approved the study according to institutional requirements.

2.2. Echocardiographic examination

A complete two-dimensional and Doppler echocardiographic exam was performed in each patient according to the criteria of the American Society of Echocardiography [8,9]. Left ventricular (LV) ejection fraction was determined using biplane Simpson's method. Left ventricular hypertrophy was defined as the Z-score of the left ventricular mass index (LVMI) being > + 2 standard deviations (SD) [10]. Dilatation of the LV or left atrium (LA) was defined as a Z-score > + 2SD [8,9]. BSA was calculated using the Mosteller formula [11]. Diastolic function was evaluated and analyzed as previously described including left ventricular inflow pattern, Doppler tissue imaging (including the E/e' ratio), the isovolumic relaxation time and the pulmonary venous flow reversal velocity [12,13].

The severity of valvular regurgitation and stenosis was determined according to ASE-guidelines [14]. Pulmonary hypertension was measured non-invasively and defined as an estimated systolic pulmonary artery pressure of > 35 mm Hg.

2.3. Electrocardiogram and 24 hour ECG

An ECG was available for review in 36 patients (92%). All ECGs were analyzed for heart rate, PR interval, QRS duration, QTc duration, QRS axis, and the presence of preexcitation or AV block. A 24-hour ECG was available in 12 patients (31%).

2.4. Follow-up

Follow-up for survival analysis was obtained in 38 patients (97%) from their last echocardiographic examination until April 30, 2011 by a clinical examination at our institution. One patient was lost to follow-up after referral to another center, where his follow-up data were not further accessible after he reached adulthood.

2.5. Statistical analysis

Categorical variables were compared using chi-square analysis (two-sided exact significance). Continuous variables were expressed as mean ± 1 SD or as median with range and were compared using the Kruskal-Wallis test. All statistical analysis was two-tailed with a p-value of < 0.05 to indicate statistical significance. Overall survival was analyzed using Kaplan–Meier curves using the log-rank test. Expected survival of an age and sex matched US-population was calculated using the Kaplan-Meier curves using the log-rank test. The severity of valvular regurgitation and stenosis was determined according to ASE-guidelines [14]. Pulmonary hypertension was measured non-invasively and defined as an estimated systolic pulmonary artery pressure of > 35 mm Hg.

3. Results

A detailed summary of the exact type of LSD, the number of patients and the age at the echocardiographic exam is shown in Table 2. MPS was the most common LSD occurring in 25 patients (64%), whereas 8 patients (21%, 7 female) had AFD. The remaining 6 patients (15%) had oLSD. The largest groups among the MPS were MPS I (Hurler disease, 7 patients) and MPS Iva (6 patients).

3.1. Clinical characteristics

Clinical characteristics are shown in Table 3. There was no significant difference in median age, median body weight and gender between the 3 groups. A heart murmur was present in 49% of patients. Most patients were in NYHA class I. One patient of the oLSD group (20%) was in NYHA class III. Signs of heart failure were observed in 3 patients with MPS (1 with MPS, 2 with MPS VI) and in the patient with DD.

In 7 patients (18%) functional class could not be assessed because of orthopedic problems. In the remaining 32 patients, there was no statistically significant difference in NYHA classification between the 3 groups.

3.2. Echocardiographic findings

A completely normal echocardiographic exam was present in 4 of 25 patients with MPS (16%), 7 of 8 patients with AFD (88%) and in the patient with M. Pompe (17% of oLSD). Echocardiographically detectable changes are summarized in Tables 4 and 5. LV dilatation was rare and LV hypertrophy was found in MPS patients (20%), in AFD patients (88%) and in oLSD patients (33%), but not in AFP patients (p = 0.56). The patient with DD had massive left ventricular hypertrophy with a left ventricular muscle mass index of 533 g/m2 (Fig. 1). All echocardiographic findings are shown in Tables 4 and 5.

Table 2

| Diagnosis                  | No. pts | Age at most recent echo (years) |
|----------------------------|---------|--------------------------------|
| MPS I: Hurler              | 7       | 2, 4, 6, 10, 11, 13             |
| MPS I: Scheie              | 1       | 16                              |
| MPS II: Hunter             | 4       | 13, 15, 16, 19                  |
| MPS Ila/b                  | 4       | 7, 11, 16, 19                   |
| MPS Iva                    | 6       | 3, 9, 11, 12, 13                |
| MPS VI                     | 2       | 9, 10, 17                       |
| Total                      | 25      |                                 |

MPS = mucopolysaccharidosis; AFD = Anderson Fabry disease; ML = mucolipidosis; PD = Pompe disease; DD = Danon disease; ICD = I-cell disease.

Table 1

| Diagnosis                  | LVH   | Diastolic dysfunction | Valvular HD | AV block | Preexcitation | VPCs/VTs or SCD | PHT |
|----------------------------|-------|-----------------------|-------------|----------|---------------|-----------------|-----|
| MPS [7,19,31]              | +     | +                     | ++          | +        | –             | –               | –   |
| AFD [4,11,28,29,34]        | +     | ++                    | +           | –        | –             | –               | +   |
| PD [47]                   | +     | +                     | –           | +        | –             | –               | +   |
| DD [24,25]                | +     | +                     | –           | –        | –             | +               | –   |
| ML II (ICD) [48]          | +     | +                     | –           | –        | –             | –               | –   |
| ML III [21]               | ?     | +                     | +           | –        | –             | –               | –   |
| Sphingolipidosis: Gaucher [40] | +   | +                     | –           | –        | –             | –               | –   |

MPS = mucopolysaccharidosis; AFD = Anderson Fabry disease; ML = mucolipidosis; ICD = I-cell disease; + = rare; ++ = common; +++ = very common; - = not described; ? = unknown.

Please cite this article as: Mueller P, et al, Cardiac disease in children and young adults with various lysosomal storage diseases: Comparison of echocardiographic and ECG changes among clinical groups, J Clin Heart Vessels (2013), http://dx.doi.org/10.1016/j.jchv.2013.10.002
Significant pulmonary hypertension was only seen in MPS (2/9, 22%). None of AFD and oLSD had non-invasively measured significant pulmonary artery pressures except for the patient with DD, who had an additional intracavitary pressure gradient in the right ventricle. There was no significant difference in the presence of diastolic dysfunction between the groups.

Valvular heart disease was frequent in MPS (76%) and oLSD (67%) as shown in Table 5. There was no difference between the presence of mitral or aortic valvular heart disease. In MPS, mitral valve (p = 0.001) and aortic valve abnormalities (p = 0.006) were significantly more commonly seen than in oLSD or in AFD.

Figs. 2 and 3 show typical mitral valve abnormalities in a 18 years old woman with MPS I and a 14 years old boy with MPS II.

### 3.3. ECG findings

An ECG was available in 36 of 39 patients. The findings are summarized in Table 6. There was no significant difference in age at ECG, heart rate, PR interval, QRS duration and QTc duration or ventricular arrhythmias between the groups (p = ns). There were no patients with ventricular tachycardias. ECG abnormalities included one 2nd degree AV block in one MPS; no higher degree AV blockage was found in our patient cohort. The patient with DD was diagnosed with a WPW syndrome. Other ECG parameters did not show any differences between the groups.

### 3.4. Treatment

Enzyme replacement therapy (ERT), was used in 13 patients (33%) suffering of MPS [9], AFD [3] or PD [1]. Bone marrow transplantation (BMT) was used in 6 patients (15%) with MPS I. There was no specific therapy for patients with ML or DD. No patient was under cardiac medication.

A summary of treatment for the LSD in these patients and the follow-up information is shown in Table 7.

### 3.5. Follow-up

Median time of clinical follow-up after the first contact with the Children’s University Hospital was 5.8 years (up to 22.2 years). Eight patients (21%) died during the follow-up period. Three deaths of the oLSD (50%) group had a diagnosis of ML II (2 deaths) and DD. One of each MPS group I, II, III, Illa and VI died (5/24 (21%) patients with a regular follow-up). The patient with MPS I was under ERT. Although ventricular dilatation and/or abnormal function were present in 3 of the patients who died subsequently, none of them died directly from heart failure or sudden cardiac death. Causes of death were respiratory failure in 7 patients and septicaemia in one patient. 30 patients (79%) were alive at the end of the follow-up period, including all patients who had undergone BMT and all patients of the AFD group. All findings about therapy and outcome are listed in Table 6. Five-year survival was 92% for MPS-, 100% for AFD- and 67% for oLSD-patients; there was no statistical significant difference between the groups (Fig. 4).

### 4. Discussion

Cardiovascular changes are frequently found in a pediatric population with LSD. In our cohort only 31% of the patients had completely normal cardiac findings. A heart murmur (49%) and valvular heart...
disease (59%) mostly of mild degree were the most common abnormalities observed and they were almost exclusively confined to children with MPS and oLSD and not yet observed in children with AFD; this may be due to the rather young age and/or higher number of females in our AFD-group. Left ventricular hypertrophy and higher degree AV block were rare in this age group in all types of LSD.

Cardiac symptoms in this age group were rare. Despite significantly decreased survival, this was not due to cardiac disease and cardiac interventions were not necessary in any of these children and adolescents with MPS.

4.1. Differences in valvular heart disease between the lysosomal storage disorders

Valvular heart disease in LSD has been most commonly described in MPS, AFD, ML II and ML III (see Table 1). In our patients, we observed valvular heart disease in 76% of patients with MPS, in 67% of those with oLSD and in none of the patients with AFD. These findings are comparable to the literature. In a study on 28 patients with MPS, mitral valve thickening was described in 61% and aortic valve thickening in 36% [7]. In an article on cardiac manifestations of AFD in children and adolescents by Kampmann et al. [16], no heart valve changes were described. Heart valve changes in AFD can occur, they have been reported to occur in 14.6% in a registry; however, they are rarely hemodynamically significant even in adults with advanced disease [17,18].

None of our patients needed valve surgery. In the literature, valve replacement has rarely been reported. In a group of children and young adults (21 months to 25 years) with MPS, Dangel et al. described valvular lesions and/or cardiomyopathy in 72% of patients [19]. The lesions were progressive but rarely led to cardiac symptoms. Only one boy with Hunter disease had to undergo successful mitral valve replacement. Both, aortic and mitral valve replacement was reported in a 14 year old female with Gaucher disease and mucolipidosis III [20,21]. Hopefully, in the current times of increasing options of enzyme replacement therapy in LSD, valve replacement in these patients will become even more rare.

4.2. Wall thickening of the left ventricle

Left ventricular wall thickening in AFD may mimic hypertrophic non-obstructive or obstructive cardiomyopathy in an adult population [22]. To our knowledge, however, obstructive hypertrophic cardiomyopathy due to AFD has not been described in children with AFD. In our pediatric AFD patients no significant left ventricular hypertrophy was detected. In AFD, onset of left ventricular wall thickening is earlier in males than females [23]. However, none of our male infants with AFD had left ventricular hypertrophy. Left ventricular wall thickening mimicking left ventricular “hypertrophy” predominated in the MPS group and oLSD. None of our patients with any LSD had a left ventricular outflow tract obstruction. Left ventricular wall thickening can also occur in other LSD such as Danon disease and Pompe disease [24–26].

In our patients, the most impressive wall thickening was seen in the patients with Danon disease who died during follow-up. Lysosome-associated membrane protein-2 deficiency (LAMP-2 deficiency), also called Danon disease, is a rare X-linked lysosomal disorder characterized by impressive cardiomyopathy, vacuolar myopathy, and mental retardation. Danon disease may cause concentric left ventricular hypertrophy; in any male teenager with concentric LVH, especially in the presence of elevated serum hepatic enzymes and CK concentrations, and/or WPW syndrome with markedly increased voltage of the left ventricle. Rarely, left ventricular outflow tract obstruction has been described in Danon disease [27]. In patients with Danon disease timely molecular diagnosis and early consideration of heart transplantation are recommended [25].

4.3. Pulmonary hypertension

The etiology of pulmonary hypertension in patients with LSD is multifactorial: severe scoliosis, obstructive sleep apnea in MPS patients, and diastolic dysfunction are the main causes. Pulmonary hypertension was detected by echocardiography only in 2 patients, and it was not hemodynamically significant. In any patient with MPS and pulmonary hypertension, one has to think of obstructive sleep apnea as in these patients, partially degraded GAGs can accumulate also in the upper airways [27].

In our patients, sleep studies were not performed routinely.

4.4. Changes in AV conduction in lysosomal storage disorders

A short PR interval is considered typical of AFD and due to accelerated atrioventricular conduction; it is seen in 14 to 40% of patients [28,29].
Older patients with AFD may develop bundle branch block and progressive AV conduction abnormalities. In our patients, a short PR interval did not only occur in patients with AFD (in 25%) but also in MPS (26%) and oLSD (50%). Thus shortening of the PR interval is not specific for AFD.

Complete AV block can occur in MPS [30,31] and may even cause sudden cardiac death in MPS as described by Hishitani et al. [31]. In the past, the incidence of sudden death in patients with MPS was reported to be as high as 11%, thus in these patients, careful surveillance with Holter ECG is needed [32]. In one of our patients with MPS, there was 2nd degree AV block in the 24 h-ECG during daily activities. This patient died 19 years old due to respiratory infection. Complete AV block in AFD has been described in middle-aged women [33], but to our knowledge this is a rarity in children.

4.5. Impact of therapies

Nowadays, the clinical course of many children with LSD is attenuated by treatments such as ERT and BMT in MPS I; the long-term effect of which has yet to be determined. Among our patients, 6 of 7 (85%) with MPS I (Hunter) had BMT, all 7 patients with MPS I were alive at the last follow-up.

Fig. 1 (continued).

Fig. 2. Example of an 18-year old woman with mucopolysaccharidosis. This shows the apical 4-chamber view (apex down) with the arrow pointing to the thickened mitral valve. No progression or regression of valvular changes after 2 years of enzyme replacement therapy was observed. LA = left atrium; LV = left ventricle; RV = right ventricle.

Fig. 3. 14-Year old patient with mucopolysaccharidosis Type II (hunter disease). LA = left atrium; LV = left ventricle.

Please cite this article as: Mueller P, et al, Cardiac disease in children and young adults with various lysosomal storage diseases: Comparison of echocardiographic and ECG changes among clinical groups, IJC Heart & Vessels (2013), http://dx.doi.org/10.1016/j.ijchv.2013.10.002
Thirty-three percent of our patients had an ERT (3 AFD, 3 MPS I, 3 MPS II, 3 MPS VI, one PD). One 9 years old girl with MPS VI died due to respiratory failure and progressive hypoventilation subsequent to craniocervical compression myelopathy despite treatment with ERT. The safety and effectiveness of ERT for AFD, MPS I, MPS II and MPS VI, as well as for PD have been demonstrated in well-designed clinical trials, and the treatments are now commercially available throughout the world [34–45]. However, except for PD (Invasive ventilator-free survival, changes in LVMI) efficacy end points did not include cardiac function. The heart is one of the major organs affected in patients with AFD. Almost all male patients with classic AFD will develop hypertrophic cardiomyopathy if untreated. Thus cardiac disorders including conduction disturbances, valve disease and heart failure have been well documented; ERT results in a dramatic improvement in cardiac symptoms in a substantial number of patients [46]. To further assess objective cardiac benefits including reduction of cardiovascular morbidity and mortality in MPS disorders, data from large registries will be of utmost importance, due to the rarity of the individual disorders.

Thus many of these patients will hopefully reach adulthood underlining the necessity that adult cardiologists are also getting familiar with these rare diseases, although we recommend that most of these patients are followed-up in specialized centers.

### 4.6. Limitations

In our patient group, follow-up time was limited and averaged only 5.8 years. However, many patients with LSD die prematurely and do not reach adulthood, which explains part of the short follow-up. In our study, 8 patients died, one was lost to follow-up. Unfortunately, detailed analysis of diastolic function is not available in all patients, most often due to a fast heart rate or diminished echo quality due to body habitus. Also, no detailed analysis with modern techniques (speckle tracking) has been performed routinely in older studies. LSD is a rare disease, so, although these children and adolescents are all patients of a tertiary referral center, this is still a small group. Thus, comparisons between the groups are difficult to interpret.

We do not have data on polysomnography in all patients with pulmonary hypertension. Therefore, the exact etiology of pulmonary hypertension cannot be determined.

### 5. Conclusions

Echocardiographically detectable cardiovascular involvement is frequent in children with LSD. However, cardiovascular findings are rarely hemodynamically significant and mostly do not necessitate any intervention. Valvular heart disease occurs mainly in patients with MPS and oLSD but is rare in AFD. A short PR interval is a characteristic ECG abnormality. Routine repeat evaluation with echocardiography and ECG is recommended in children with LSD.

### References

[1] Wappner RS. Lysosomal storage disorders. In: McMillan JA, Feigin RD, editors. Oski's pediatrics. Principles and practice. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 2199.

[2] Cox GF. Diagnostic approaches to pediatric cardiomyopathy of metabolic genetic etiologies and their relation to therapy. Prog Pediatr Cardiol 2007;24(1):15–25.

[3] Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA 1999;281(3):249–54.

[4] Linhart A, Elliott PM. The heart in Anderson–Fabry disease and other lysosomal storage disorders. Heart 2007;93(4):528–35.

[5] Hopwood JJ, Morris CP. The mucopolysaccharidoses. Diagnosis, molecular genetics and treatment. Mol Biol Med 1990;7(5):381–404.
Maron BJ, Roberts WC, Arad M, et al. Clinical outcome and phenotypic expression in patients with mucopolysaccharidosis. Cardiol Young 2010;20(3):254–61.

Lopez L, Colon SD, Frommett P, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr 2010;23(5):405–95.

Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;8:1454–7.

Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol Feb 15 1986;57(5):450–8.

Mosteller RD. Simplified calculation of body surface area. N Engl J Med 1987 Oct 22;317(17):1098.

McMahon CJ, Nagueh SF, Pignatelli RH, et al. Characterization of left ventricular diastolic function by tissue Doppler imaging and clinical status in children with hypertrophic cardiomyopathy. Circulation 2004;109(4):1756–62.

BuLock FA, Mott MC, Martin RP. Left ventricular diastolic function in children measured by Doppler echocardiography: normal values and relation with growth. Br Heart J 1995;73(4):334–9.

Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16(7):777–802.

Therneau T and original Report by Lumley T (2009). survival: Survival analysis, in- cluding penalised likelihood. R package version 2.35–8. http://CRAN.R-project.org/

Kampmann C, Wietthoff CM, Wbyhra C, Baehner FA, Mengel E, Beck M. Cardiac manifestations of Anderson–Fabry disease in children and adolescents. Acta Paediatr 2008;97(4):463–9.

Linhart A, Kampmann C, Zamorano JL, et al. Cardiac manifestations of Anderson–Fabry disease: results from the international Fabry outcome survey. Eur Heart J 2007;28(10):1228–35.

Weidemann F, Strothmann JM, Niemann M, et al. Heart valve involvement in Fabry cardiomyopathy. Ultrasound Med Biol 2009;35(5):730–5.

Dangel JH. Cardiovascular changes in children with mucopolysaccharidosis storage diseases and related disorders—clinical and echocardiographic findings in 64 patients. Eur J Pediatr 1998;157(7):334–8.

Cindik N, Ozcay F, Sueren D, et al. Gaucher disease with communicating hydrocephalus and cardiac involvement. Clin Cardiol 2010;33(1):E26–30.

Cripe LH, Ware SM, Hinton RB. Replacement of the aortic valve in a patient with mucolipidosis III. Cardiol Young 2009;19(6):641–3.

Elliot P, Baker R, Pasquale F, et al. ACES study group. Prevalence of Anderson–Fabry disease in patients with hypertrophic cardiomyopathy: the European Anderson–Fabry Disease survey. Heart 2011;97(23):1957–60.

Kampmann C, Linhart A, Baehner F, et al. Onset and progression of the Anderson– Fabry disease related cardiomyopathy. Int J Cardiol 2008;130(3):367–73.

Balmer C, Ballhausen D, Bosshard NU, Buehler J, Schieleer S, et al. Familial X-linked cardiomyopathy (Danon disease): diagnostic confirmation by mutation analysis of the LAMP2 gene. Eur J Pediatr 2005;164(8):599–14.

Maron BJ, Roberts WC, Arad M, et al. Clinical outcome and phenotypic expression in patients with mucopolysaccharidosis. Cardiol Young 2010;20(3):254–61.

Namdar M, Kampmann C, Steffel J, et al. PQ interval in patients with Fabry disease. Am J Cardiol 2010;105(5):753–6.

Toda Y, Takeuchi M, Morita K, et al. Complete heart block during anesthetic management in a patient with mucopolysaccharidosis type VII. Anesthesiology 2001;95(4):1035–7.

Hishitani T, Wakita S, Isoda T, Katori T, Ishizawa A, Okada R. Sudden death in Hunter syndrome caused by complete atrioventricular block. J Pediatr 2000;136(2):268–9.

Krovetz J, Schiebler G. Cardiovascular manifestations of genetic mucopolysaccharidoses. Virchol Dtsch 1972:8:192.

Dai Y, Toda G, Yano K. Siblings with atypical Fabry’s disease with complete atrioven- tricular block. Heart 2003;89(1):e2.

Spada M, Chiappa E, Ponzoni A. Cardiac response to enzyme-replacement therapy in Gaucher’s disease. N Engl J Med 1998;339(16):1165–6.

Schiffmann R, Kopp JB, Austin III HA, Sabnis S, Moore DF, Weibel T, et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA 2001;285(21):2743–9.

Eng CM, Banikazemi M, Gordon RE, et al. A phase 1/2 clinical trial of enzyme replacement in Fabry disease: pharmacokinetic, substrate clearance, and safety studies. Am J Hum Genet 2001;68(3):711–22.

Eng CM, Guffon N, Wilcox WR, et al. Safety and efficacy of recombinant human alpha-galactosidase A—replacement therapy in Fabry’s disease. N Engl J Med 2001 Jul 5;345(1):9–16.

Wilcox WR, Banikazemi M, Guffon N, et al. Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. Am J Hum Genet 2004;75(1):65–74.

Banikazemi M, Bultas J, Waldek S, et al. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. Am Intern Med 2007;146(2):77–86.

Kakkis ED, Muenzer J, Tiller GE, et al. Enzyme-replacement therapy in mucopolysaccharidosis I. N Engl J Med 2001;344(3):182–8.

Wraith JE, Clarke IA, Beck M, et al. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-1-iduronidase (laronidase). J Pediatr 2004;144(5):581–8.

Harmatz P, Giugliani R, Schwartz IV, et al. Enzyme replacement therapy in mucopolysaccharidosis VI (Maroteaux–Lamy syndrome). J Pediatr 2004;144(5):574–80.

Muenzer J, Gussacivas-Caliologu M, McCandless SE, Schuetz T, Kimura A. Phase I/II clinical trial of enzyme replacement therapy in mucopolysaccharidosis II (Hunter syndrome). Mol Genet Metab 2007;90(3):329–37.

Kishnani PS, Corto D, Niculino M, et al. Recombinant human acid [alpha]-glucosidase: major clinical benefits in infantile-onset Pompe disease. Neurology 2007;69(2):196–99.

Harmatz P, Giugliani R, Schwartz I, et al. Enzyme replacement therapy for mucopolysaccharidosis VII: a phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human N-acetylgalactosamine 4-sulfatase (recombinant human aroylsulfatase B) and follow-on, open-label extension study. J Pediatr 2006;148(4):533–9.

Mehta A, Beck M, Sunder-Plassmann G, editors. In. Fabry disease: perspectives from 5 years of ROS. Oxford: Oxford PharmaGenesis; 2006.

Kishnani PS, Howell RR. Pompe disease in infants and children. J Pediatr 2004;144(5 Suppl):S35–43.

Sato Y, Sakamoto K, Fujibayashi Y, et al. Cardiac involvement in mucolipidosis. Importance of non-invasive studies for detection of cardiac abnormalities. Jpn Heart J 1983;24(1):148–59.

Roseggarten D, Abrahamow A, Nir A, et al. Outcome of ten years’ echocardiographic follow-up in children with Gaucher disease. Eur J Pediatr 2007;166(5):549–5.