Heart and Vessels (2019) 34:290–295
https://doi.org/10.1007/s00380-018-1242-1

ORIGINAL ARTICLE

Aortic root dilatation in patients with mucopolysaccharidoses and the impact of enzyme replacement therapy

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Received: 12 March 2018 / Accepted: 17 August 2018 / Published online: 22 August 2018

Abstract

Mucopolysaccharidoses (MPS) are disorders characterized by impaired glycosaminoglycan (GAG) catabolism as a consequence of a deficiency or the absence of lysosomal enzymes directly involved in their degradation. Multiple organ systems are involved in MPS, including the cardiovascular system. Recently, aortic root dilatation (ARD) has been described in these patients. Thus, we reviewed aortic root diameter measurements in 69 MPS patients from a single center from 2000 to 2016. Aortic root diameter *z* scores were calculated based on data published by Colan et al. according to the body surface area (BSA) determined using the Haycock formula. The overall incidence of ARD in MPS patients was 39.1%. Higher mean *z* scores were present in patients with MPS IVA and VI when compared to MPS I and II. Aortic root *z* scores were higher in older MPS IVA patients, which may suggest a progressive ARD change in this MPS type. No significant differences were found before and after enzyme replacement therapy (ERT) in 11 patients with available data (2 with MPS I; 4 with MPS II; 2 with MPS IVA, and 3 with MPS VI). This work provides further evidence that ARD is common in different types of MPS, being especially evident in MPS IVA, but with a significant occurrence also in MPS VI.

Keywords Aorta · Mucopolysaccharidoses · Enzyme replacement therapy · Dissecting aneurysm

Introduction

Mucopolysaccharidoses are characterized by impaired glycosaminoglycan (GAG) catabolism resulting from a deficiency in lysosomal enzymes directly involved in their degradation. Eleven different MPS disorders are currently described in humans, each with a different enzyme defect. Five main types of GAG accumulation occur in MPS patients depending on the enzyme defect: heparan sulfate, dermatan sulfate, keratan sulfate, chondroitin sulfate, and hyaluronan.

The severity of MPS I and II is well defined; patients with a severe phenotype present cognitive decline. In MPS IV and VI, some patients present more rapid deterioration than others, but cognitive abnormalities are not usually found. Cardiovascular problems are among the main manifestations observed in patients with both severe and attenuated phenotypes, being described in all MPS types except MPS IX. Furthermore, cardiovascular problems, respiratory infections, and restrictive pulmonary disease are among the main causes of mortality [1].

The great vessels may be affected in MPS by thickening of their walls and can be constricted or dilated. Histological abnormalities that are observed in the aortic walls include aortic wall thickening, accumulation of GAGs, and disruption of elastin fibers [2–4]. ARD is frequently found in animal models of MPS I, resulting in the effacement of the sinotubular ridge [2]. Although initial analyses failed to find the same pattern of ARD in humans [2], more recent studies have identified that ARD may also occur in MPS patients, especially those with MPS IVA [5–8].

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Enzyme replacement therapy (ERT) has been available for MPS I, II, and VI since the mid-2000s, and more recently approved for MPS IVA and MPS VII. However, studies in animal models suggest that the recombinant enzyme often fails to reach the aorta and thus has limited impact on this aspect of the disease [9, 10].

Therefore, we aimed to assess ARD occurrence and patterns in a larger sample of patients with different types of MPS collected over the last 16 years. In addition, we assessed the impact of enzyme replacement therapy on the aortic dilatation observed in these diseases.

Materials and methods

Data collection

Following institutional ethical approval, we performed a chart review of patients with MPS that had performed echocardiograms from January 2000 to June 2016. In all cases, we used only the measurement obtained at the sinus of Valsalva (SoV). Aortic root diameter *z* scores adjusted for BSA were calculated as previously described [11] and confirmed using the method of Dallaire et al. [12]. BSA was determined using the Haycock formula [13]. Aortic root dilatation was defined as a *z* score ≥ 2.0.

For comparison between MPS types, only the last echocardiogram of the patients was included in the analysis. All patients with more than one available echocardiogram were included in the analysis of *z* score variation over time.

Patients with available measurements before ERT (up to 5 years before ERT was started) and at least 8 months after that date (up to 5 years after ERT was started) were analyzed for the assessment of pre- and post-treatment *z* scores.

Statistical analysis

All data were entered into PASW Statistics 18.0 for Windows (SPSS Inc., Chicago, IL, USA) and subjected to specific statistical analyses. *Z* score distribution was assessed with the Shapiro–Wilk and Kolmogorov–Smirnov tests, and as normal distributions were observed, parametrical tests were used in all subsequent analyses. Mean *z* score comparisons between MPS groups were calculated using ANOVA with Tukey's post hoc test. Linear regression and Pearson's correlation coefficient were used to assess *z* score variation over time. *Z* score variation over time for individual patients with each type of MPS was assessed using a mixed model analysis corrected for treatment status (with or without ERT), including all patients with more than one available echocardiogram. A paired *t* test was used to compare pre- and post-treatment *z* scores. Bonferroni correction was used for multiple comparisons. A p value ≤ 0.05 was considered significant.

Results

A total of 69 patients with MPS were included (25 with MPS I, 21 with MPS II, 16 with MPS IVA, and 7 with MPS VI) (Table 1). In total, 27 of the 69 patients (39.1%) met the criteria for ARD. Higher mean *z* scores were present in patients with MPS IVA and VI when compared to MPS I and II (Table 1). ARD was found more frequently in the former group. Among patients with MPS I, 5 (20.0%) met the criteria for ARD, and 6 (28.6%), 11 (68.8%), and 5 (71.4%) for MPS II, MPS IVA and MPS VI, respectively (Fig. 1). Moreover, patients with the severe MPS I phenotype had higher *z* scores when compared to those with an attenuated phenotype (Fig. 2).

Aortic root *z* scores were higher in older MPS IVA patients, which may suggest that ARD is progressive in

Table 1 Demographic characteristics and aortic root measurements among MPS patients

	Overall ($N=69$)	MPS I ($n=25$)	MPS II ($n=21$)	MPS IVA ($n=16$)	MPS VI ($n=7$)	p
Age (years)	14.4 (9.9)	14.6 (12.1)	13.0 (9.1)	15.8 (8.9)	15.0 (5.4)	0.852
Weight (kg)	30.5 (16)	30.9 (19.3)	35 (16.6)	25.6 (9.3)	27.1 (11.8)	0.333
Height (cm)	114.7 (21.1)	117.5 (27.3)	122.3 (17.4)	102.2 (9.7)	110 (11.3)	0.023[a]
BSA (m^2)	1 (0.3)	1 (0.4)	1.1 (0.3)	0.9 (0.2)	0.9 (0.2)	0.206
SoV (cm)	2.3 (0.4)	2.2 (0.4)	2.3 (0.4)	2.5 (0.4)	2.3 (0.4)	0.137
z score	1.7 (1.6)	1.1 (1.6)	1.2 (1.4)	3.1 (1.5)	2.1 (1.1)	0.001[b]

Values are mean (±SD)

BSA body surface area. *SoV* aortic root diameter at the sinus of Valsalva

[a]MPS IVA different from the other groups

[b]MPS IVA and VI are different from MPS I and II

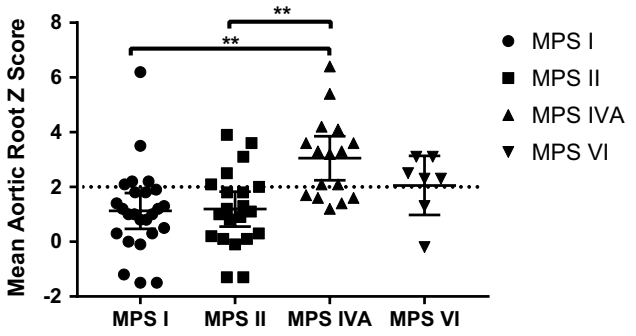

Fig. 1 Mean aortic root diameter in different MPS types. Only the final measurement was included in this analysis. $^{**}p < 0.01$. ANOVA and Tukey's post hoc

this type of MPS (Fig. 3c). The mean MPS IVA *z* score increase was 0.058 per year (95% CI 0.004–0.113). A positive linear regression slope was also observed in the MPS VI group, but the correlation was not statistically significant (Fig. 3d).

An inverse correlation was observed between aortic root *z* scores and age in MPS I and MPS II (Fig. 3a, b), but this may be due to the presence of attenuated phenotypes in the older patients. When only including patients with severe phenotypes, we did not observe a significant change with age, which is possibly due to the small number of patients (data not shown).

Pre- and post-ERT *z* score data were available for 11 patients (2 with MPS I; 4 with MPS II; 2 with MPS IVA, and 3 with MPS VI). There was no statistically significant variation in the *z* scores between the two periods ($p = 0.697$; Figs. 4a–d). For all of the presented analyses, comparable results were obtained when using the Dellaire et al. [12] method to calculate *z* scores (data not shown).

Discussion

In this study, we evaluated aortic root diameter in 69 patients with MPS, which represents the largest collection of MPS patients to date. Our results confirm previous reports showing a significant proportion of MPS patients with ARD (39.1% in this study; 35.3% of 36 patients in a previous report [8]). In addition, we report for the first time that a large proportion of MPS VI patients have aortic dilatation. Considering that MPS are progressive disorders, aortic pathology is also expected to be progressive. However, variation in aortic root diameter over time was not observed in the mixed models analysis for any of the MPS types (data not shown). This may reflect either a slow progression rate, which could not be measured in our sample, or the fact that aortic root diameter ceases to dilate beyond a certain point. Supporting the former hypothesis, aortic root *z* scores were higher in older patients, at least in MPS IVA. This finding is consistent with a previous report identifying a correlation between age and aortic root dimensions in MPS IVA [6].

We confirmed that ARD is found predominantly in patients with the severe MPS I phenotype (Hurler syndrome) [5], which may explain the inverse correlation between age and *z* scores in these patients. Hurler syndrome is characterized by developmental delay/intellectual disability. Somatic manifestations are also more severe in these patients, especially when compared to the most attenuated phenotype (Scheie syndrome). Some patients are situated in the middle of the spectrum with more prominent somatic involvement and little-to-no intellectual dysfunction, which is classified as Hurler–Scheie syndrome. A binary classification of severe (Hurler syndrome) and attenuated (Hurler–Scheie and Scheie syndromes) phenotypes is also used. As patients with the severe phenotype have a lower life expectancy, older MPS I patients are mostly represented by those with the

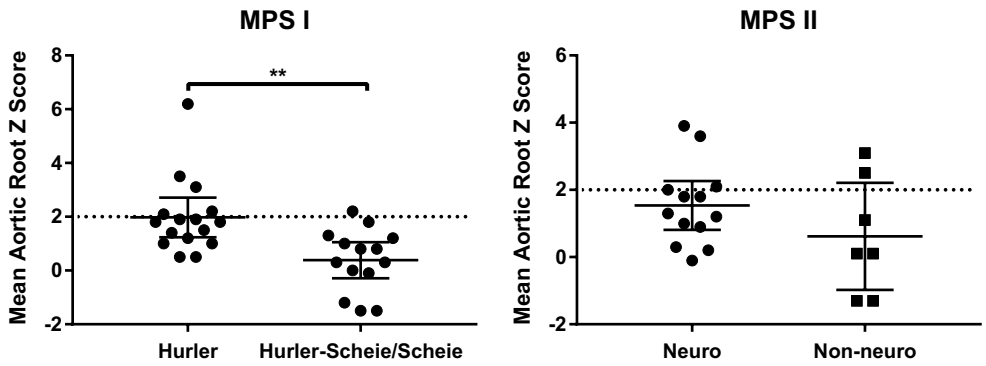

Fig. 2 Aortic diameter according to disease severity. Mean aortic root diameter is higher in MPS I patients with Hurler (severe) than Hurler–Scheie and Scheie (attenuated) phenotypes. In MPS II, there is no significant difference in aortic root diameter between neuronopathic and non-neuronopathic patients. Only the final measurement was included in this analysis. $^{*}p < 0.05$, Student's *t* test

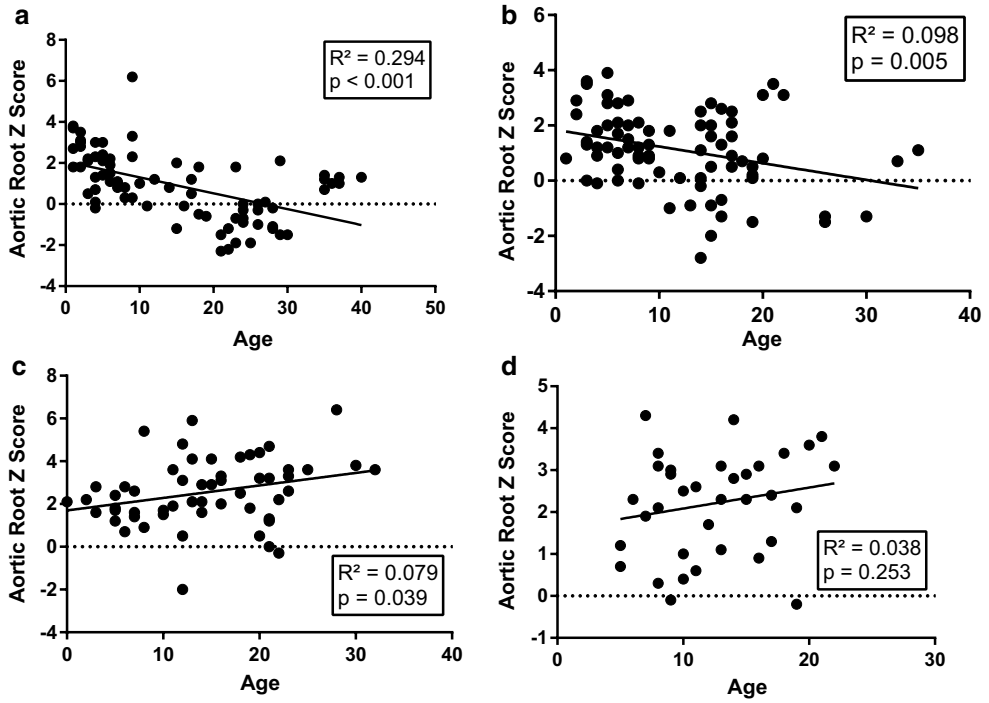

Fig. 3 Aortic root dilation versus age. Aortic root diameter *z* score values at different ages in MPS I (**a**), MPS II (**b**), MPS IVA (**c**), and MPS VI (**d**). Multiple measures were obtained from the same patients at different ages when available

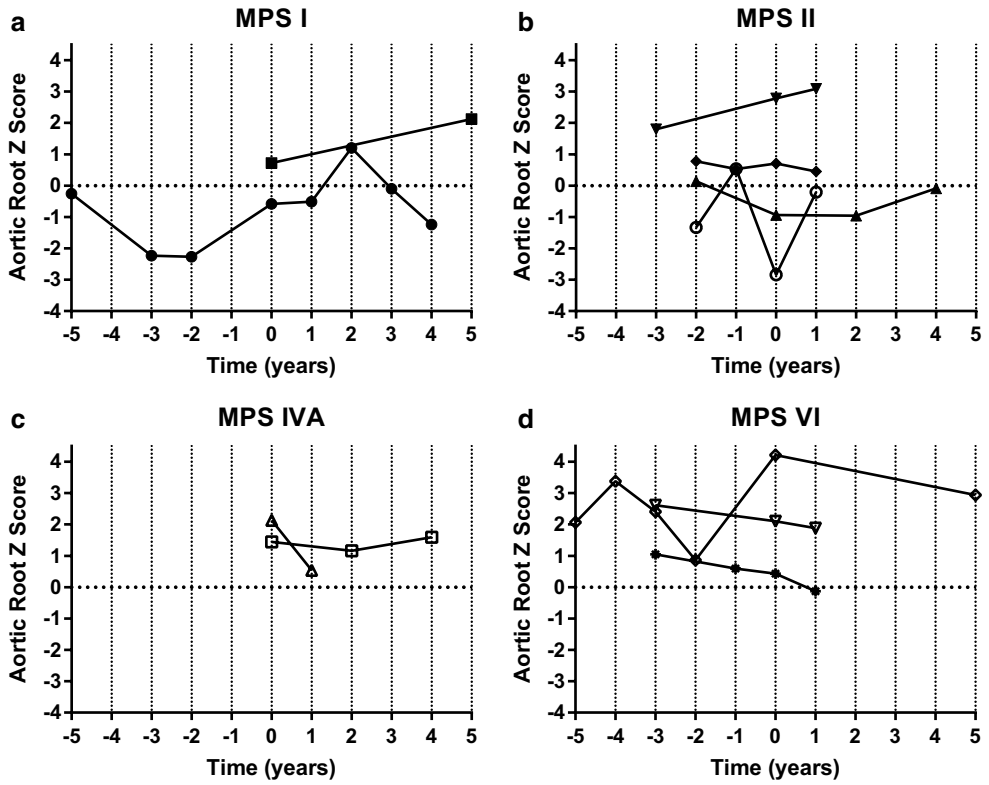

Fig. 4 Impact of ERT on aortic root diameter. Aortic root diameter *z* scores for single patients before and after ERT in MPS I (**a**), MPS II (**b**), MPS IVA (**c**), and MPS VI (**d**)

attenuated phenotype who would also be expected to have a less prominent involvement of the aorta [14].

No significant association was observed between aortic root diameter and disease severity in MPS II patients. A similar pattern was found along the severity spectrum (Fig. 2). Similar to MPS I, the classification of the disease in MPS II depends on the presence (neuronopathic form) or absence (non-neuronopathic form) of intellectual disability. Furthermore, as in MPS I, patients with the neuronopathic form have more severe somatic involvement. In fact, increased somatic burden and decreased neurocognitive ability were shown to be correlated even in patients with attenuated MPS I and MPS II phenotypes [15]. Thus, it is reasonable to believe that the same association identified in MPS I is also present in MPS II patients, although this could not be clearly demonstrated herein.

ARD identification has clinical importance, as it may progress to aortic dissection [16]. Aortic dissection generally occurs in older patients (mean age 62 years), although it may occur earlier in high-risk groups, including patients with Marfan or Turner syndromes [17, 18]. Although MPS patients have not been shown to be at increased risk for this uncommon life-threatening condition, it is known that the GAG content increases in dissecting aneurysms of the thoracic aorta in humans [19, 20].

Currently, elective aortic surgery is indicated for adult patients with an aortic root diameter ≥ 55 mm with the objective of preventing aortic dissection [21]. In Marfan syndrome, the threshold for this indication is 50 mm, and in the presence of additional risk factors (i.e., family history of dissection, progressive dilatation > 2 mm/year, severe aortic or mitral regurgitation, and desire for pregnancy) it is reduced to 46 mm [22]. While recommendations for surgery based on z score values are lacking, it is generally assumed that a value < 4.0 does not represent an imminent risk for aortic dissection [18]. In their cohort, Bolourchi et al. [8] did not observe any case of aortic dissection. This complication was also not observed in this study and only one MPS I and four MPS IVA patients had z scores > 4.0 (Fig. 1). None of our patients had an absolute aortic root dimension greater than 45 mm.

We did not observe any effect of ERT on aortic root measurements. This is in accordance with findings of other authors [6, 8]. However, in the case of MPS IVA, this evaluation can be especially difficult because ERT was only recently approved [6]. While it is still unclear if ERT can prevent or treat ARD in MPS patients, studies in mouse models demonstrate that this abnormality can be responsive to losartan [23]. The same medication also promotes improvements in left ventricle diameter, shortening, fraction, and craniofacial aspects in animal models [23, 24].

This work has some limitations. Although this is the largest cohort of MPS patients reported to-date, the aortic root measurement was not performed in the controlled environment of a clinical trial due to retrospective data being used. Furthermore, for a single patient, different echocardiographers were involved during the follow-up period, which may have affected the results. Regardless, our results are consistent with the literature. Another limitation is that we relied on echocardiography data to obtain the aortic root measurements (as other published studies in patients with MPS have). The use of more precise methods, such as cardiac MRI, may allow more robust analyses of the entire thoracic aorta. Nevertheless, risks related to sedation in young children should be considered. Finally, using z score parameters in short-stature patients may likely overestimate the parameter, pointing to the existence of aortic dilatation in a setting where the growth of the aorta is similar to age-matched individuals, although disproportional to the patient's height and thorax dimensions. In Turner syndrome, a condition in which both aortic root dilatation and short stature are observed, a disease-specific parameter was recently developed [25]. As there is no such parameter for MPS, we managed to reduce this bias using an additional multivariate formula recently published and used for Turner syndrome [12, 26]. The results were unaffected.

In summary, this work supports evidence that ARD is a clinical manifestation of different types of MPS. It also confirms that this finding is particularly prominent in MPS IVA patients. Moreover, it identifies a significant involvement in patients with MPS VI for the first time. ERT did not reduce aortic diameters, and ancillary therapies, such as the use of losartan, may be needed for MPS patients with aortic dilatation.

Funding We thank the Isaac Foundation and Conselho Nacional de Desenvolvimento Científico (CNPq) for funding this study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal informed consent is not required.

Research involving human and/or animal participants This article does not contain any animal studies performed by any of the authors.

References

1. Tan CT, Schaff HV, Miller FA, Edwards WD, Karnes PS (1992) Valvular heart disease in four patients with Maroteaux-Lamy syndrome. Circulation 85:188–195

2. Braunlin EA, Harmatz PR, Scarpa M, Furlanetto B, Kampmann C, Loehr JP, Ponder KP, Roberts WC, Rosenfeld HM, Giugliani R (2011) Cardiac disease in patients with mucopolysaccharidosis: presentation, diagnosis and management. J Inherit Metab Dis 34:1183–1197
3. Yasuda E, Fushimi K, Suzuki Y, Shimizu K, Takami T, Zustin J, Patel P, Ruhnke K, Shimada T, Boyce B, Kokas T, Barone C, Theroux M, Mackenzie W, Nagel B, Ryerse JS, Orii KE, Iida H, Orii T, Tomatsu S (2013) Pathogenesis of Morquio A syndrome: an autopsied case reveals systemic storage disorder. Mol Genet Metab 109:301–311
4. Lew V, Pena L, Edwards R, Wang RY (2017) Cardiovascular histopathology of a 11-year old with mucopolysaccharidosis VII demonstrates fibrosis, macrophage infiltration, and arterial luminal stenosis. In: Morava E, Baumgartner M, Patterson M, Rahman S, Zschocke J, Peters V (eds) JIMD reports, vol 39. Springer, Berlin, pp 31–37
5. Schroeder L, Orchard P, Whitley CB, Berry JM, Tolar J, Miller W, Braunlin EA (2013) Cardiac ultrasound findings in infants with severe (Hurler phenotype) untreated mucopolysaccharidosis (MPS) type I. JIMD Rep 10:87–94
6. Kampmann C, Abu-Tair T, Gökce S, Lampe C, Reinke J, Mengel E, Hennermann JB, Wiethoff CM (2016) Heart and cardiovascular involvement in patients with mucopolysaccharidosis type IVA (Morquio-A syndrome). PLoS One. https://doi.org/10.1371/journal.pone.0162612
7. Bolourchi M, Chen Y, Renella P, Nguyen DV, Wang R (2016) Aortic root dilatation in mucopolysaccharidosis. Mol Genet Metab 117:S29
8. Bolourchi M, Renella P, Wang RY (2016) Aortic root dilatation in mucopolysaccharidosis I–VII. Int J Mol Sci. https://doi.org/10.3390/ijms17122004
9. Jurecka A, Tylki-Szymańska A (2015) Enzyme replacement therapy: lessons learned and emerging questions. Expert Opin Orphan Drugs 3:293–305
10. Baldo G, Wu S, Howe RA, Ramamoothy M, Knutsen RH, Fang J, Mecham RP, Liu Y, Wu X, Atkinson JP, Ponder KP (2011) Pathogenesis of aortic dilatation in mucopolysaccharidosis VII mice may involve complement activation. Mol Genet Metab 104:608–619
11. Colan SD, McElhinney DB, Crawford EC, Keane JF, Lock JE (2006) Validation and re-evaluation of a discriminant model predicting anatomic suitability for biventricular repair in neonates with aortic stenosis. J Am Coll Cardiol 47:1858–1865
12. Dallaire F, Bigras J-L, Prsa M, Dahdah N (2015) Bias related to body mass index in pediatric echocardiographic Z scores. Pediatr Cardiol 36:667–676
13. Haycock GB, Schwartz GJ, Wisotsky DH (1978) Geometric method for measuring body surface area: a height–weight formula validated in infants, children, and adults. J Pediatr 93:62–66
14. Beck M, Arn P, Giugliani R, Muenzer J, Okuyama T, Taylor J, Fallet S (2014) The natural history of MPS I: global perspectives from the MPS I Registry. Genet Med 16:759–765
15. Ahmed A, Shapiro E, Rudser K, Kunin-Batson A, King K, Whitley CB (2016) Association of somatic burden of disease with age and neuropsychological measures in attenuated mucopolysaccharidosis types I, II and VI. Mol Genet Metab Rep 7:27–31
16. Weinsaft JW, Devereux RB, Preiss LR, Feher A, Roman MJ, Basson CT, Geevarghese A, Ravekes W, Dietz HC, Holmes K, Habashi J, Pyeritz RE, Bavaria J, Milewski K, LeMaire SA, Morris S, Milewicz DM, Prakash S, Maslen C, Song HK, Silberbach GM, Shohet RV, McDonnell N, Hendershot T, Eagle KA, Asch FM, Registry Investigators GENTAC (2016) Aortic dissection in patients with genetically mediated aneurysms: incidence and predictors in the GenTAC Registry. J Am Coll Cardiol 67:2744–2754
17. Nienaber CA, Fattori R, Mehta RH, Richartz BM, Evangelista A, Petzsch M, Cooper JV, Januzzi JL, Ince H, Sechtem U, Bossone E, Fang J, Smith DE, Isselbacher EM, Pape LA, Eagle KA, International Registry of Acute Aortic Dissection (2004) Gender-related differences in acute aortic dissection. Circulation 109:3014–3021
18. Carlson M, Silberbach M (2009) Dissection of the aorta in Turner syndrome: two cases and review of 85 cases in the literature. BMJ Case Rep. https://doi.org/10.1136/bcr.06.2009.1998
19. Humphrey JD (2013) Possible mechanical roles of glycosaminoglycans in thoracic aortic dissection and associations with dysregulated transforming growth factor-β. J Vasc Res 50:1–10
20. Jain D, Dietz HC, Oswald GL, Maleszewski JJ, Halushka MK (2011) Causes and histopathology of ascending aortic disease in children and young adults. Cardiovasc Pathol 20:15–25
21. Kim EK, Choi SH, Sung K, Kim WS, Choe YH, Oh JK, Kim D-K (2014) Aortic diameter predicts acute type A aortic dissection in patients with Marfan syndrome but not in patients without Marfan syndrome. J Thorac Cardiovasc Surg 147:1505–1510
22. Endorsed by the Association for European Paediatric Cardiology (AEPC), Authors/Task Force Members, Baumgartner H, Bonhoeffer P, De Groot NMS, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJM, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E, ESC Committee for Practice Guidelines (CPG), Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas P, Widimsky P, Document Reviewers, McDonagh T, Swan L, Andreotti F, Beghetti M, Borggrefe M, Bozio A, Brecker S, Budts W, Hess J, Hirsch R, Jondeau G, Kokkonen J, Kozelj M, Kucukoglu S, Laan M, Lionis C, Metreveli I, Moons P, Pieper PG, Pilossoff V, Popelova J, Price S, Roos-Hesselink J, Uva MS, Tornos P, Trindade PT, Ukkonen H, Walker H, Webb GD, Westby J (2010) ESC guidelines for the management of grown-up congenital heart disease (new version 2010): the task force on the management of grown-up congenital heart disease of the European Society of Cardiology (ESC). Eur Heart J 31:2915–2957
23. Gonzalez EA, Tavares AMV, Poletto E, Giugliani R, Matte U, Baldo G (2017) Losartan improves aortic dilatation and cardiovascular disease in mucopolysaccharidosis I. J Inherit Metab Dis 40:311–312
24. Osborn MJ, Webber BR, McElmurry RT, Rudser KD, DeFeo AP, Muradian M, Petryk A, Hallgrimsson B, Blazar BR, Tolar J, Braunlin EA (2017) Angiotensin receptor blockade mediated amelioration of mucopolysaccharidosis type I cardiac and craniofacial pathology. J Inherit Metab Dis 40:281–289
25. Quezada E, Lapidus J, Shaughnessy R, Chen Z, Silberbach M (2015) Aortic dimensions in Turner syndrome. Am J Med Genet A 167A:2527–2532
26. Alami Laroussi N, Dahdah N, Dallaire F, Thérien J, Fournier A (2016) Aortic dilatation in patients with Turner's syndrome without structural cardiac anomaly. Cardiol Young 26:539–546