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Original Article

Marfan syndrome associated aortic disease in neonates and children: a clinical–morphologic review

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ABSTRACT

Background: Marfan syndrome (MFS) is a multisystem connective tissue disorder that can lead to aortic dilation requiring aortic root replacement. Neonatal MFS (nMFS) is a rare and severe form of MFS compared to classic MFS (cMFS). Aortic root histology in MFS is thought to demonstrate predominantly medial degeneration (MD) of a translamellar mucoid extracellular matrix accumulation (MEMA-T) vs. the intralamellar mucoid extracellular matrix accumulation (MEMA-I) seen in other aortopathies. The objective of this study was to describe the clinical and histopathologic features of nMFS and cMFS patients undergoing aortic root replacement.
Methods: Children with MFS who underwent aortic root replacement between 2000 and 2012 at a single institution were included. Medical records including clinical details, aortic dimensions (*Z* scores), and histology including MD type were obtained. Statistics were descriptive with univariate analysis of age at surgery and type of MD.
Results: Eleven patients, 3 (27%) with nMFS, were included. Root dilation at time of surgery was greater in nMFS compared to cMFS ($Z = 12.8$ vs. 7.6, $P = .005$), and nMFS patients were younger at time of surgery (7.3 vs. 18.8 years, $P = .002$). Histology in the nMFS group demonstrated MEMA-I in one and no MD in two. In the cMFS group, there were three with MEMA-T, four with MEMA-I, and one with both types.
Conclusion: In summary, nMFS has earlier root dilation often in the absence of MD. Both forms of MD were present in our cohort, and there was no correlation between age at surgery and type of MD.

1. Introduction

Marfan syndrome (MFS) is an inherited, multisystem disease of connective tissue associated with an autosomal dominant mutation of the fibrillin gene (*FBN1*) [1]. Diagnosis of MFS is based on clinical criteria known as the Ghent nosology [2]. MFS is associated with pathologic findings in the cardiovascular, ocular, and skeletal systems and less commonly the lungs, dura, and skin. Clinical manifestations of MFS, particularly the musculoskeletal manifestations, become more apparent with increasing age; however, it can be diagnosed in the neonatal period [3,4]. Neonatal MFS (nMFS) is associated with a more severe phenotype and increased morbidity and mortality compared to classic MFS (cMFS) [3,5–7]. Both nMFS and cMFS have cardiovascular manifestations consisting of mitral valve dysfunction and dilation of the ascending aorta [8,9]. Aortic dilation is present in 35% of patients prior to 5 years of age and up to 70% of patients prior to 20 years of age [10]. Aortic pathology often necessitates surgical measures including aortic root replacement during childhood [11].

Histologic analysis of the aortic root in MFS has classically been associated with varying degrees of medial degeneration (MD), including mucoid extracellular matrix material accumulation, elastic fiber fragmentation (EFF), and varying degrees of smooth muscle cell nuclei loss (SMCNL) representative of apoptosis [12–14]. MD of the ascending aorta has been identified in the ascending aorta in nMFS, but there is a paucity of data regarding the aortic histologic changes in nMFS [7]. MFS has been characterized by MD which spans several individual elastic fiber-smooth muscle lamellar units of the aortic media or translamellar mucoid extracellular matrix accumulation (MEMA-T). This pattern of MD has been proposed as a feature that may help distinguish MFS from other inherited connective tissue disorders, particularly Loeys–Dietz syndrome (LDS) [15]. In LDS, the extracellular matrix accumulation tends to occur within individual lamellar units or intralamellar mucoid extracellular matrix accumulation (MEMA-I) [13,15].

Little is known regarding the differences in aortic pathology between patients with nMFS and cMFS. The objective of this study was to compare the clinical and pathologic characteristics (especially type of MD) of patients with nMFS and cMFS who underwent aortic root replacement in a single institution. Additionally, we sought to evaluate the clinical characteristics of patients exhibiting MEMA-T and MEMA-I pathology.

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2. Methods

All consecutive patients with MFS followed at Primary Children's Hospital that had undergone aortic root replacement between 2000 and 2012 were included in the study. Patients were identified using the computerized Marfan Clinic Database at Primary Children's Hospital. Clinical diagnosis of MFS was based on the 2010 Ghent nosology, and each MFS diagnosis was retrospectively confirmed based on clinic notes and imaging studies [2]. We excluded patients with clinical or genetic evidence of other aortopathies including LDS. Patients were classified as nMFS if the diagnosis occurred during the first year of life and cMFS if the diagnosis occurred ≥1 year. Specific details of diagnosis including family history (MFS diagnosis in a first-degree relative) and any *FBN1* mutation testing were recorded.

2.1. Imaging

Imaging studies were reviewed, and aortic valve, aortic root, sinotubular (ST) junction, and ascending aorta measurements were obtained from the last echocardiogram or cardiac magnetic resonance imaging (MRI) prior to the operative procedure. In cases where echocardiogram and MRI measurements occurred on the same day, the MRI measurement was used. As anatomic measurements in pediatric patients vary based on age and size, *Z* scores are frequently used. *Z* scores describe standard deviations from a previously established mean based on the patients' BMI, with negative and positive numbers representing the number of standard deviations below or above a specific measurement, respectively [16]. All imaging measurements were converted into *Z* scores.

2.2. Histology

Pathologic specimens were obtained from surgical samples obtained during aortic root replacements. Because of the small size of the majority of these specimens, they were submitted in their entirety, and selective sampling was not necessary. However, there was a single case of cMFS where only three small fragments were received. Specimens were stained with hematoxylin and eosin (H&E) and elastic Van Gieson stains using standard laboratory protocols. All specimens were analyzed for the predominant pattern of MD with two types of MD identified: MEMA-T and MEMA-I. MEMA-T was defined as an increase in mucoid matrix that alters the arrangement of lamellar units (Fig. 1 and Table 1: case 9). MEMA-I was defined as an increase in mucoid matrix that does not alter that arrangement (Fig. 2 and Table 1: case 5). EFF was also evaluated semiquantitatively and defined as increased gaps in the elastic fiber meshwork surrounding the lamellar units with increasing translamellar spaces (Table 1: case 1) [13]. Smooth muscle cell nuclei loss was defined as medial areas devoid of the typical elongated nuclei of vascular smooth muscle cells [12]. The degree of each of these medial degeneration changes was semiquantitatively graded on a scale of 0 to 4+ based on the extent of medial involvement and severity in the most affected area of the artery as described previously [15]. All pathologic specimens were reevaluated as part of this study, and determination of type and severity of medial degeneration was completed by a single cardiovascular pathologist.

2.3. Statistics

Descriptive statistics including mean and range were used to summarize results. Continuous variables including aortic root size at time of surgery between nMFS and cMFS patients and age at time of surgery for patients with pathologic findings of MEMA-T and MEMA-I were compared using unpaired Student's *t* test with two-tailed distribution.

3. Results

Eleven patients with MFS underwent aortic root replacement between 2000 and 2012. There were 5 males (45%). All patients were Caucasians, with 2 (18%) ethnic Hispanics. A diagnosis of MFS was established in all patients using the modified Ghent nosology with diagnostic criteria for each patient listed in Table 1. Mean age at diagnosis was 11 years (0–22 years) for the entire cohort. nMFS was diagnosed in 3 (27%) patients and cMFS in 8 (73%). All three of the nMFS patients were diagnosed during the initial hospitalization. The 8 patients with cMFS were diagnosed at mean age of 18 years (range: 13–22 years). Ten (91%) patients were on medications at the time of surgery, with 4 (40%) patients on angiotensin-converting enzyme inhibitors and 6 (60%) patients on beta-blockers. One (9%) patient with cMFS was referred to surgery soon after initial presentation and was not started on medications prior to surgery.

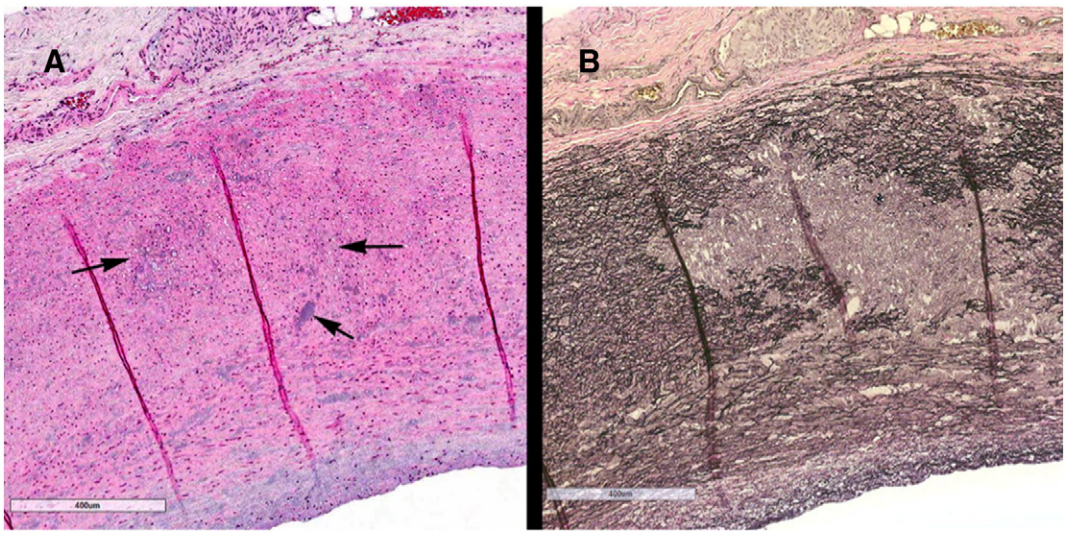

Fig. 1. (A) Photomicrograph showing an example of translamellar mucoid extracellular matrix accumulation (MEMA-T) with arrows indicating pools of pale blue mucopolysaccharide in the aortic media (H&E). (B) Photomicrograph of the corresponding elastic stain highlighting MEMA-T with complete loss of elastic fibers and accumulation of mucopolysaccharide spanning numerous lamellar units (elastic Van Gieson stain).