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Aortic aneurysm/dissection and osteogenesis imperfecta: Four new families and review of the literature

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ABSTRACT

Osteogenesis imperfecta (OI) is the commonest form of heritable bone fragility. It is mainly characterized by fractures, hearing loss and dentinogenesis imperfecta. OI patients are at increased risk of cardiovascular disease of variable severity. Aortic aneurysm/dissection is one of the rarer but potentially serious cardiovascular complications of OI. So far, only six patients with aortic dissection and OI have been reported. As such, present OI diagnostic guidelines do not recommend systematic screening of patients for aortopathy. Here, we report on the clinical and molecular characteristics of three new OI patients and one additional patient with a first degree relative who presented with aortic dissection and/or aneurysm surgery. This observation further opens up the discussion on the need for and extent of cardiovascular screening in adult patients with OI.

1. Introduction

Since the creation of the International Registry of acute Aortic Dissection (IRAD), a wealth of information has been gathered on the epidemiology and pathogenesis of ascending aortic dissection. Risk factors and comorbidities that emerged are male sex, age 60–70, pregnancy, cocaine abuse, hypertension, prior cardiac surgery or aortic dissection, atherosclerosis, diabetes, bicuspid aortic valve and connective tissue disorders such as Marfan syndrome.

Osteogenesis imperfecta (OI, [MIM166200-166210-166220-259420-259440-301014-610682-610915-610967-610968-613848-613849-613982-614856-615066-615220-616229-616507-617952]), also known as brittle bone disease, refers to a group of phenotypically and genetically heterogeneous connective tissue disorders most prominently characterized by multiple fractures leading to skeletal deformity and/or short stature, dentinogenesis imperfecta, hearing loss and blue sclerae. In over 85% of patients, OI is an autosomal dominant disorder caused by heterozygous mutations in *COL1A1* [MIM120150] or *COL1A2* [MIM120160] encoding respectively the α1(I) and α2(I) chains of type I collagen [1]. Discovery of recessive genes has resulted in a newer understanding about OI genetics, with about 20 different genetic causes, in addition to type 1 collagen genes now accounting for a total of approximately 95% of cases [2]. The classification of OI has evolved over time corresponding to the newly identified genes. Traditionally, the diagnosis was mostly based on clinical evaluation and radiographic findings. However, with increased access to genetic testing and advances in genomic sequencing, genetics evaluation is now playing a key role in the diagnosis of OI.

A recent systematic review of the relevant literature pointed out that patients with OI are at increased risk of cardiovascular disease [3]. The association between OI and cardiovascular abnormalities has been known for years, but the precise spectrum and incidence of cardiovascular abnormalities has only been described a few times. An increased incidence of valvular heart disease is best established, with aortic and mitral regurgitation being the most commonly described OI-related valvular insufficiencies. This may be due to the result of biomechanical

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difference and type 1 collagen properties, although this is not certain based on evidence so far. From 70 published OI patients, 40 cases (57%) showed aortic valve insufficiency and 24 (34%) mitral valve insufficiency [3–5]. Conversely, reports of aortic dissection in patients with OI are rare. Aortic dissection in the setting of OI was first described in 1993 by Ashraf et al. [6]. Since then, five more cases have been published [7,8]. Ashraf et al. suggested that mechanical weakness secondary to abnormal type I collagen in the aortic wall might underlie OI-related aortic dissection, especially because cases lacked any other known predisposing cause for aortic dissection [6]. Subsequent case reports assume the same pathogenic mechanism [7,8].

Here, we present three OI patients and one other OI patient with a first degree relative with aortic aneurysm and/or dissection, ascertained independently from three international clinical centers specializing in OI diagnosis and management. We discuss the association between OI and cardiovascular complication with potential impact of early cardiovascular screening in adults with OI.

2. Materials and methods

Peripheral blood was drawn from each patient for gDNA extraction and subsequent diagnostic testing for mutations in known OI and aortic aneurysm and/or dissection genes. OI genetic testing involved Sanger sequencing of *COL1A1* and *COL1A2* (patients 1–2) per standard protocol or gene panel sequencing (patients 3–4) of all or some of the listed OI genes (Supplementary Table 1). Genetic testing for thoracic aortic aneurysm and/or dissection (TAAD) involved gene panel sequencing of 28 genes (patients 1–4; Supplementary Table 1). An aortic biopsy was also undertaken in patient 2. All participants gave informed consent for the study and the protocol was approved by the local ethics committees.

The literature review on the concomitant presentation of OI and aortopathy was based on a Pubmed database search executed independently by two researchers using “osteogenesis imperfecta” and either “aortopathy”, “aneurysm” or “dissection” as search terms.

3. Results

3.1. Patient 1

This 46-year old female presented with short stature (151 cm), relatively short arms, blue sclerae and a round face, but no other obvious clinical features of OI. She suffered three leg bone fractures during infancy but has not been on OI-related therapy. At age 45, she had an aortic type B dissection (distal arch to renal artery) in the absence of common risk factors: she was a non-smoker and there was no evidence for hypertension or hyperlipidemia. A strong family history of OI was reported, with five relatives being diagnosed with OI to date (Supplementary Fig. 1A). Aortic dissection was not reported in any of these. Molecular genetic testing for OI identified a *COL1A2* pathogenic variant (c.2305G > C; p.Gly769Arg; https://oi.gene.le.ac.uk/home.php?select_db=COL1A2) affecting a triple helix glycine residue in both the proband and her affected sister. The proband's sister is short (153 cm), has relatively short arms and blue sclerae in addition to a round face, and suffered from recurrent leg and shoulder fractures during childhood. TAAD gene panel sequencing was negative.

3.2. Patient 2

This 37-year old male had two OI-related surgeries for fractures of his right elbow and two for fractures of his right knee. He did not have other OI-related treatments. He suffered from aortic and mitral valve endocarditis at the age of 35, which resulted in a double mechanical valve replacement. A year later, the patient presented with dyspnoea caused by paravalvular leakage of the aortic valve prosthesis. Significant partial dehiscence of the prosthesis was noted. Aortic and mitral valve replacement were performed in the assumption that the mitral valve would also be infected, but all cultures performed on blood and resected material (postoperatively) were negative. The aortic root demonstrated significant dilatation (47 mm) that required replacement. The aortic wall had a different macroscopic appearance compared to a year earlier, with the wall being whiter in colour and the sinuses markedly stretched. An aortic biopsy confirmed degenerative medial changes with elastic fiber fragmentation and accumulation of glycosaminoglycans. Cardiovascular risk factors included smoking (ex-smoker, three pack-years). A family history of cardiovascular disease was excluded, as well as diabetes mellitus, arterial hypertension, renal insufficiency, other vascular disease. A clinical diagnosis of OI was confirmed by the identification of a *COL1A1* c.104-2A > G pathogenic variant. This mutation affects the canonical splice site and is predicted to diminish splice efficiency. With the exception of fractures in his son (with the *COL1A1* mutation), there was no family history of OI. TAAD gene testing was negative.

3.3. Patient 3

This 42-year old female with a clinical diagnosis of type 1 OI is adopted with no children of her own. She has greyish white sclerae and a normal adult stature. She had a fractured wrist at 12 years of age and developed a hip fracture as an adult. Owing to osteoporosis which was confirmed on DEXA scan, she was started on vitamin D and calcium supplements. Nonetheless, she went on to suffer fractured tibia, totalling up to five low trauma fractures. At age 41, she suffered a type A aortic dissection, which was successfully repaired. She is a non-smoker and there was no clinical evidence for hypertension, hyperlipidemia or any other significant cardiovascular risk factors. Valvular function was normal. OI genetic testing was negative, but TAAD gene analysis identified a heterozygous deletion of the 128 bp-containing exon 7 of *TGFBR2* [MIM190182]. The deletion is predicted to lead to a premature stop codon because of a frameshift event and, hence, likely results in nonsense mediated mRNA decay (NMD) [9]. Truncating *TGFBR1/2* mutations that undergo NMD are classically not considered causal for aneurysmal disease. We therefore currently classify this deletion as a variant of unknown significance (VUS).

3.4. Patient 4

This 48-year old female with type 1 OI, ten fractures during child- and adulthood, blue sclerae and mild hearing loss presented herself seeking advice regarding her chances of developing OI-related cardiovascular complications. Her sister, niece and father were also diagnosed with OI (Supplementary Fig. 1B). The latter died from aortic dissection (type unknown) at age 47. No further family history of aneurysmal disease was reported. The proband is not on OI treatment, however, she has asthma for which she is on salbutamol inhalers. Echocardiography showed a normal heart structure and aortic diameters. The clinical OI diagnosis was confirmed by molecular genetic testing, which showed a pathogenic single nucleotide deletion c.614delC leading to a frameshift mutation (p.Pro205Leufs*60) in *COL1A1* (https://oi.gene.le.ac.uk/home.php?select_db=COL1A1). TAAD genetic testing in the proband revealed a VUS in *MYH11* (c.418G > A, p.Asp140Asn; [MIM160745]; https://www.ncbi.nlm.nih.gov/clinvar/variation/426591/).

4. Discussion

Major clinical manifestations in OI are bone fragility and fractures. However, other type 1 collagen-rich tissues, like the skin, sclerae, teeth, blood vessels, tendons and ligaments can also be affected. OI is thus associated with a wide spectrum of symptoms, representing a challenge when counselling OI patients. The majority of OI cases have a heterozygous mutation in either *COL1A1* or *COL1A2*, the genes encoding the two chains of type 1 procollagen. Collagen type 1 constitutes nearly 80% of the total collagen in the myocardium and 80–90% of the

Table 1
Patients with aortic dissection from literature.

Sex	Age	History of HT	Aortic phenotype	Valve phenotype	OI phenotype	Genetic testing	Reference
M	39	No	Type I dissection with aortic root 60 mm	Severe AR, other valves normal	Deafness, blue sclerae, multiple fractures – type I	ND	Ashraf, 1993 [6]
M	32	ND	Type I dissection with ascending aorta 40 mm	Normal valves	Normal hearing, blue sclerae, kyphoscoliosis, recurrent fractures with long bone deformity – type I	ND	Moriyama, 1995 [8]
M	54	ND	Type A dissection	At age 39, aortic valve replacement	Multiple recurrent fractures – type I	ND	Cusimano, 1996 [13]
M	65	Yes	Type A dissection	At age 47, aortic valve surgery At age 50, aortic and mitral valve surgery	OI – type I or IV	ND	Isotalo, 1999 [14]
M	44	ND	Type III-B dissection with descending aorta of 48 mm	Normal valves	Blue sclerae, bilateral tibial bowing, scoliosis - Type Ia	ND	Byra, 2008 [15]
M	34	ND	Type A dissection with dilated aortic root and ascending aorta	Severe AR, BAV	OI – type non-specified	ND	McNeeley, 2012 [7]

Abbreviations: AR – Aortic regurgitation, BAV – bicuspid aortic valve, HT – hypertension, ND – not determined, OI – osteogenesis imperfecta.

collagen found in the aorta are types I and III. Hence, it is biologically plausible that defects in collagen I production may cause cardiovascular abnormalities. Cardiovascular involvement in OI is well recognized. Compared to aortic and mitral valve involvement, OI-related aortic aneurysm and dissection are rare. Of note, the medical literature on aortic aneurysm and dissection in OI as such is scarce (Table 1) but there is more data providing evidence of aortic root dilatation in patients with OI (Table 2).

An extensive Danish literature study showed increased risk for cardiovascular disease in OI cases [3]. Aortic dilatation was reported to be amongst the most common OI-associated cardiovascular manifestations. The data available on aortic root measurements are variable, but with exception of one study all reported studies have shown that OI patients have larger aortic root measurements than age and BSA-matched controls (Table 2).

Overall, 10–30% of OI patients have aortic Z-scores above 2 or present with dissections [3,10,11]. Dilatation is already present at a young age as evidenced by three pediatric studies [3,11,12]. Interestingly, several studies suggest that type III/IV OI patients have more pronounced aortic root dilatation [11,12]. Unfortunately, we do not have data on the aortic sizes prior to dissection in our series.

All previously described cases of OI-related aortic dissection were discussed from a surgical management point of view, revealing that only one of the cases had a type B dissection and the remainder a type A dissection [8]. The underlying molecular diagnosis in these cases had not been reported. In the current paper, we describe four new patients with aortic dissection and/or aneurysm surgery. From these case descriptions, interesting observations emerged. Firstly, we report on the first OI females with aortic dissection. The patients reported so far were all males, while our study identified two females. Remarkably, when reviewing the published literature on OI-related aortic dilation, nearly every study had included more males than females, suggesting that OI males might be more susceptible for dissection compared to females, which would be in keeping with general risk factors for aortic dissection. Further studies are warranted to confirm this. Secondly, for the first time we report on aortic dissection in molecularly confirmed OI. In our study we identified a *COL1A2* glycine substitution, a *COL1A1* splice site mutation and a *COL1A1* single nucleotide deletion resulting in a frameshift event. Thus, there seems to be no specific collagen I mutation subtype predisposing to aortic aneurysm/dissection. Except for a VUS in *TGFBR2* and *MYH11*, no variants were identified in the known TAAD genes. Although we cannot exclude a contributing effect of these two variants, from a biological perspective both seem benign. The *TGFBR2* deletion is predicted to lead to NMD and this would preclude a role in aneurysm formation. It is likely that Patient 3 has a rare form of OI for which the gene is currently unknown or current testing has not identified a type 1 collagen variant. However, this patient clearly phenotypically has OI.

Moreover, the *MYH11* variant is not located in the functionally important coiled-coiled domain, making a pathogenic effect very unlikely. It is thus more plausible that the type 1 collagen mutations cause or increase risk for the aneurysm/dissection phenotype in OI. Although in literature it has been suggested that aortic dilatations are more pronounced in OI type III/IV, the currently reported patients seem to fit more within the type I spectrum based on clinical classification. Both type A and B dissections occur in OI, but as in the non-OI population, type A dissection seems more common. Finally, it has been suggested that dissections in OI patients might be related to arterial hypertension. Several of our patients (patients 1–3) were not hypertensive though.

Taken together, the presented families point in the direction of a link between OI and aortic dissection. It is important to highlight that all four families had a clinical presentation of type 1 OI and clinically very similar in their phenotypes despite their molecular results. An important question is whether or not this link is significant enough to recommend standard cardiovascular/aneurysm screening in all adult OI patients. We are aware that some international centers offer

Table 2
Literature summary on aortic dilation in osteogenesis imperfecta.

Study population	Result	Reference
20 probands (15 females/5 males) (Age 13–67 years; mean) (OI type I: 17, OI type III/IV:3)	Enlarged mean aortic diameter 31.9 mm vs 27 mm BSA normalized also increased	White et al., 1983 [16]
66 probands from 109 families (36 females, 30 males) (Age 1–74 years)	12.1% (8/66) have aortic dilatation > 127% of age- and weight predicted dimension	Hortop et al., 1986 [10]
58 pediatric patients (Age 2–16 years) OI type I: 18, OI type III:25, unclassified: 15	Normal aortic diameter range in type I 28% of aortic diameters in type III > +2 SD	Vetter et al., 1989 [11]
40 probands with OI (21 female, 19 male) (Mean age 40 years) (OI type I: 35, III/IV: 5)	No significant difference (22.7 mm vs 22 mm)	Migliaccio et al., 2009 [17]
26 OI patients (19 female, 7 male) (Mean age 38.8 years) 70% mild OI	Significant larger aortic root diameters (27 mm vs 25 mm) (also after normalisation for BSA)	Jimenez et al., 2010 [18]
99 probands Norway (57 female, 41 male) (Age 25–83 years, mean 43.9 years) OI type I: 77; OI type III/IV: 21	Mild absolute increase but p < 0,05 when BSA normalized (29.5 mm vs 28.6 mm or 18.6 mm/m^2 vs 15.4 mm/m^2)	Radunovic et al., 2011 [19]
24 probands with mean age 58 months	Ascending aorta 25.3 mm/m^2 vs 17.7 mm/m^2 (p < 0,01)	Karamifar et al., 2013 [20]
8 patients with type III/IV OI (5 females/3 males) (3–12 years)	Increased aorta sinus Z-score (p = 0,001) Increased ascending aorta Z-score (p = 0,001)	Al-Senaidi et al., 2015 [21]
70 patients (pooled from case reports and small series)	19% history of aortic dissections and aneurysms	Ashournia et al., 2015 [3]
100 pediatric patients (55 females/45 males) (5–20 years) (Type I: 44; Type III/IV: 54)	Sinuses of Valsalva (22.4 mm vs 21.5 mm) More evident in the OI type III/IV subgroup (p < 0.001)	Rush et al., 2017 [12]

Abbreviations: BSA – Body surface area, OI – osteogenesis imperfecta, SD – standard deviation.

cardiovascular screening in the form of 3–5 yearly echocardiograms, especially in adults, but there is no consensus on recommended cardiac surveillance in OI. To find evidence-based answers on this subject, larger studies on the prevalence of aortic dissection and risk factors for dissection in OI populations should be performed. This research might also help to stratify OI patients and identify high risk patients that would benefit from routine cardiovascular surveillance. For now, initial cardiovascular screening at diagnosis in the form of echocardiogram and regular screening of valve function and aortic diameters depending on initial screening seems appropriate in OI patients.

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Author contributions

Study design: MB, HM, GM and BL. Study conduct: AV1, SK, SS and IR. Data collection: MB, GM, AV1, SK, IL, MP, SS, HK, AV2, IR, LvL and BL. Data analysis: MB, AV1, SK, SS, GM, HM and BL. Data interpretation: MB, HK, LvL, AV2 and BL. Drafting manuscript: MB, AV1, SK, HK, AV2 and BL. Revising manuscript content: IL, MP, and LvL. Approving final version of the manuscript: MB, GM, AV1, SK, IL, MP, SS, HM, IR, LvL, AV2 and BL. MB takes responsibility for the integrity of the data analysis.

Competing interests

We do not have any conflict of interest to declare.

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