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CASE REPORT

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Autosomal recessive cutis laxa type Ib—Successful redo aortic root and arch replacement

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Abstract

We present an adolescent girl with a highly stenotic ascending aortic conduit of her former during infancy corrected giant aneurysm. Genetic testing determined *autosomal recessive cutis laxa type-Ib* as the underlying connective tissue disorder. Re-do valve sparing root and arch replacement gained excellent restoration of the aorta; 1-year-follow-up was uneventful.

KEYWORDS

aortopathy, cutis laxa, fibulin-4, valve sparing root replacement

1 | INTRODUCTION

Several connective tissue disorders leading to often fatal aortic dissections are mostly caused by sporadic or autosomal dominant inherited mutations.[1] A rare exception is the syndromic autosomal recessive cutis laxa type Ib (ARCL-Ib), an aortopathy or even arteriopathy which is often perinatally lethal.[2] This disease is caused by pathogenic variants in the endothelial growth factor (EGF)-containing fibulin-like extracellular matrix protein 2 (EFEMP2) gene.[3] These loss-off function mutations lead to reduced production of fibulin-4, which is essential in cross-linking of elastin monomers during elastogenesis.[4] Fibulin-4 compounds six areas of calcium binding (cb-) EGF-like motifs, four with the typical 6-cysteine-binding arrangements, and a calcium binding complex in each cb-EGF-like motif, identically found in fibrillin-1.[5] Most known pathological missense mutations of *EFEMP2* induce changes in these disulfide- or calcium binding areas,[6] with detrimental impact on elastogenesis by reducing and/or disrupting elastic fiber assembly. Hence, extreme tortuosity and fusiforme dilatations of nearly all large and medium sized arteries and likewise veins can occur. Often, the cutis laxa, although eponymous for this

disease, is not specifically pronounced.[5] Further, ARCL-Ib patients can present arterial stenosis either of the peripheral pulmonary arteries and/or in the aortic isthmus. Very often, marked left ventricular hypertrophy is existent. In the severe and perinatally lethal form, patients often manifest pulmonary emphysema and/or hernia or rupture of the diaphragm. Bone fractures or joint dislocations, arachnodactyly, and facial dysmorphisms are often described; further on, presentation of microcephalism and/or mental retardation is common.[7]

2 | CASE REPORT

2.1 | History of presentation

A 15-years-old girl with a history of a 45 mm ascending aortic aneurysm during infancy, replaced uneventfully by a 16 mm graft as a valve sparing root replacement (VSRR), presented now, 14 years later. On echo, marked left ventricular hypertrophy, a severely stenotic aortic conduit, and ante-position of her head and neck arteries with a 40 mm dilated succeeding aortic arch and additionally mild pulmonary artery stenosis were depicted and further verified on CT (Figure 1A–D). On cerebral MR-angiography, tortuous and elongated cerebral arteries and significant dilatations of her jugular veins were present (Figure 1E–F), indicating a systemic connective tissue disorder of the arterial tortuosity spectrum. Physical examination proved mild doughy skin and a relatively short and obese status (10th height percentile, 95th weight percentile, 60th head circumference percentile). During infancy, a bilateral clubfoot operation was performed, no further bone or joint problems were reported. Normal motor functions, but slightly lower intellectual capacity was stated but with regular secondary school education.

Family history illustrated four children from an unaffected, consanguine couple. The oldest, apparently healthy son has discontinued contact with the family. The second child, a 17-years-old daughter is likewise clinically healthy and attending grammar school. Remarkably, the third child died suddenly in his infancy in hospital during examinations for his microcephaly, epilepsy, and mental retardation. Immediate resuscitation efforts were abortive, postmortem autopsy revealed a giant ascending aneurysm and aortic coarctation, which was considered

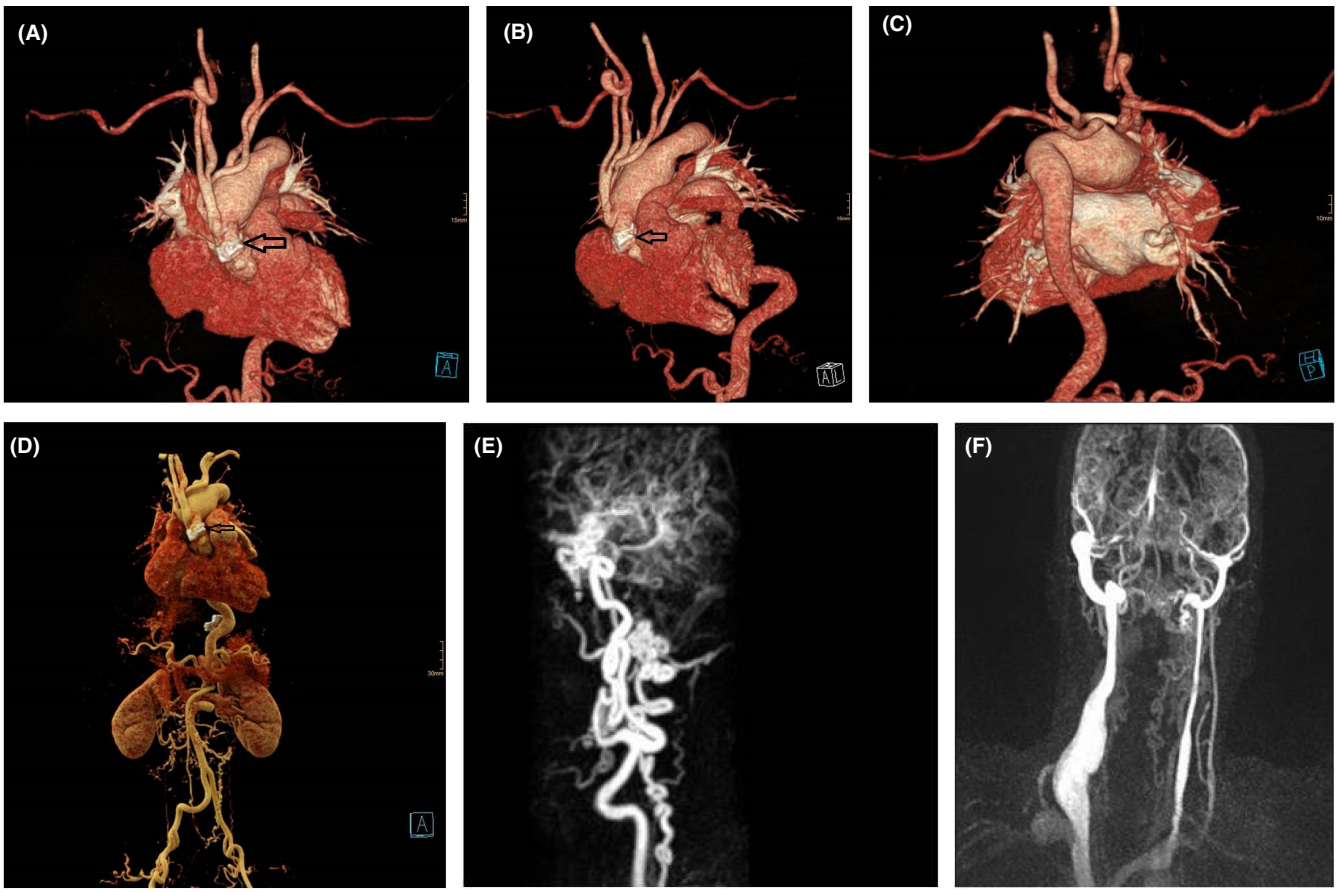

FIGURE 1 (A–D) 3D-CT reconstruction of the aorta. Representing the stenotic conduit (black arrows) and the adjacent dilated aorta. (E,F) MR-angiography of the supra-aortic arteries

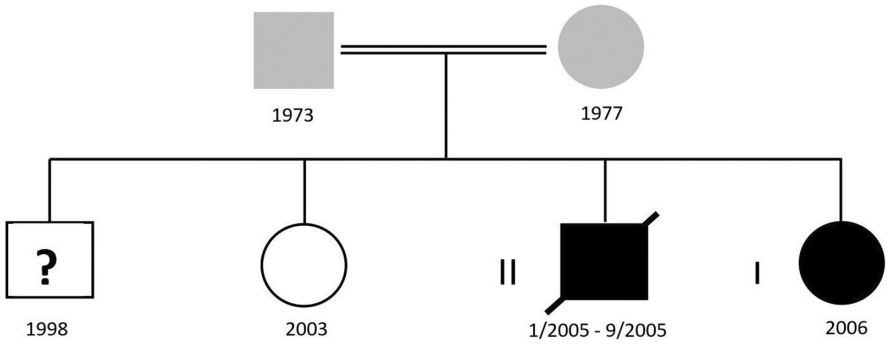

FIGURE 2 Family-Pedigree. Numbers indicating year of birth (lifespan); square: male; circle: female; crossed out: deceased; black: homozygous mutation; gray: heterozygous mutation; achromatic: not affected. I: reported patient; II: deceased brother

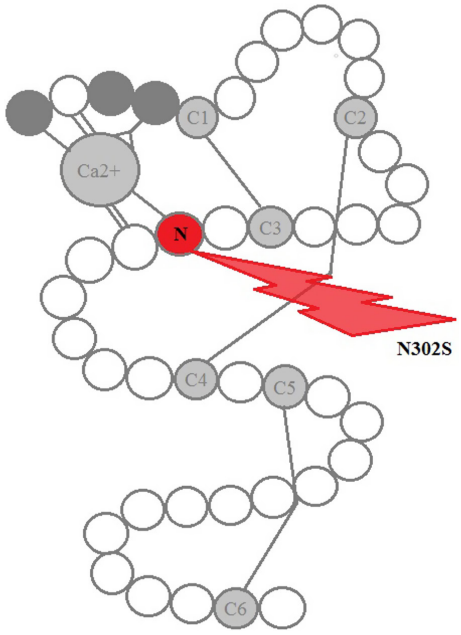

FIGURE 3 Draft of the cb-EGF-like domain of EFEMP2. The flash indicating the ascertained mutation in the family (N: asparagine; S: serine).

causative. Genetic investigation revealed a variant of unknown significance (VUS) in the cyclooxygenase type II (COX-2) gene only. The fourth child, our patient, was born short-time after her older brother's decease (Figure 2).

2.2 | Medical investigations

Whole-exome analysis was performed after enrichment with the TruSeq Exome Kit (Illumina). DNA fragments were paired end sequenced on an Illumina NextSeq500 system and assessed using VarSeq software (GoldenHelix). A novel homozygous missense mutation in the *EFEMP2* gene (c.905A>G; NM_016938.5) in exon 9 (p.Asn302Ser) at an essential calcium binding location was found (Figure 3). The asparagine residue at codon 302 of *EFEMP2* is conserved in all mammalian species. Further, the formerly encountered VUS in *COX-2* of her deceased brother could also be detected in the mitochondrial genome of our patient (mt.A8033G; I150V; NC_012920). Interestingly, the *EFEMP2* homozygous mutation was found in the stored DNA of her deceased brother. Both parents were heterozygous for the *EFEMP2* mutation, and the mother additionally carries the mitochondrial homoplastic VUS. The sister was tested negative for all stated variants.

2.3 | Management and follow-up

A re-do VSRR was performed: Cannulation was implemented with a 14 mm conduit to the right subclavian artery and venal cannulation to the left femoral vein. Due to the massive adhesion of the calcified conduit causing bleeding during re-sternotomy, the patient was cooled to 18°C under total cardiac arrest for inspection and hemostasis. After detachment of the former conduit, further operation was performed on pump with 25°C body temperature. Hereby, preparation of the entire thoracic aorta including head and neck vessels and inspection of the old conduit was accomplished. The aortic arch was excised and resected up to the proximal descending aorta under selective bispheric antegrade head perfusion. A 20 mm Siena™-prosthesis was trimmed and anastomosed end-to-end with the descending aorta; head and neck vessels were re-implanted using continuous suture lines. Inspection of the aortic valve proved morphologically unremarkable; therefore, the native valve was left in place and reconstruction of the sinutubular junction by using a 24 mm Gelweave™-vascular-prosthesis was performed. Anastomosis of both prostheses was followed by rewarming and weaning from the pump. Intraoperative transesophageal echocardiography depicted only minimal aortic valve regurgitation. Postoperative care was uneventful with discharge of the patient on postoperative day 10. Skin biopsy, harvested during operation, showed only minor reduction of elastic fibers (Figure 4). A postoperative CT scan proved excellent reconstruction of the aorta and aortic arch (Figure 5A,B). One-year follow-up confirmed optimal function of the heart and valves with

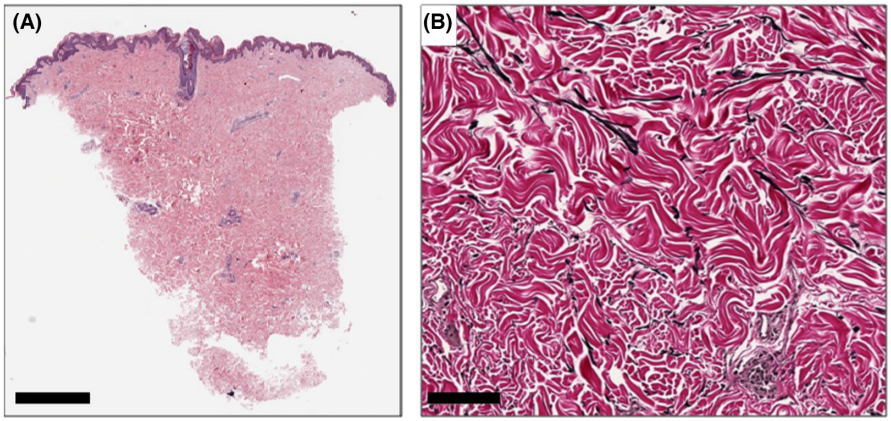

FIGURE 4 Histopathologic features of cutis laxa. (A) Punch biopsy. Regular cornified epidermis. Scant perivascular lymphocytic infiltrate in the upper dermis. H&E stain. The scale bar is 1 mm. (B) Elastic fibers (black) are scarce, partly clumped, and fragmented. EVG stain. The scale bar is 100 μm

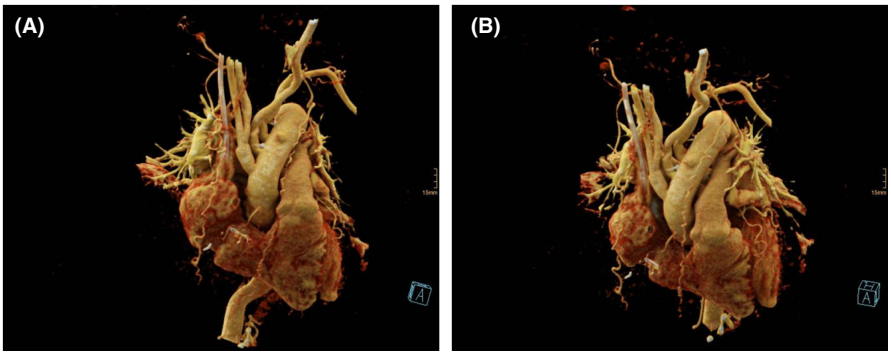

FIGURE 5 Postoperative 3D-CT reconstruction of the aorta

significant reduction of left ventricular hypertrophy and an excellent quality of life only under supportive medical treatment with the angiotensin receptor blocker losartan due to borderline blood pressure levels and her now known genetic disorder of the connected tissue.

3 | CONCLUSION

Former clinical and animal studies depicted detrimental outcome of fibulin-4 missense mutations affecting the calcium-binding site by causing perinatally lethal arteriopathy.[8] In the presented family, one infant died, retrospectively owing to sequels of this disorder, while the second child, resulting from an early diagnosis with now two successful surgical repairs, survived the otherwise probably fatal arteriopathy. The latter repair of our patient was performed by a redo-VSRR with a 24 mm Gelweave™-vascular-as well as a repair of the arch with a 20 mm Siena™-prosthesis. Due to the known tissue fragility in this specific disease as well as current age and height of our patient (nearly outgrown patient), we restrained from using autologous tissue for arch repair—as described in a previous case report.[9] Since the interaction of fibulin-4 with other matrix molecules is highly dependent on Ca^{2+}-binding,[8] this depicted novel mutation appears highly pathological. The additional mitochondrial VUS can either be non-relevant—referring to the unobtrusive presence in the mother—or a co-founder owing to its regulatory impact on vasoconstriction and vasorelaxation properties with enhanced synthesis and expression of COX-2 in already impaired contraction properties found in Marfan patients.[10] Possibly, this phenomenon may explain the borderline blood pressure levels in our patient since hypertension is not typically described in ARCL-Ib patients.

Hereinafter, these extensive genetic investigations clarified the former unknown cause of the partially lethal and progressive connective tissue disorder in this family, consequently, thorough surveillance from head to pelvis for emerging aneurysm formation in these patients is mandatory.

AUTHOR CONTRIBUTIONS

CP has initiated the investigations, taken care of the case, managed the treatment, and drafted the manuscript. DZ has performed the operation and reviewed the manuscript. SR has performed the histological investigation and reviewed the manuscript. DB has accomplished the imaging and reviewed the manuscript. IMB has organized and supervised the treatment, edited, and revised the manuscript. FAL performed the genetic testing and edited and revised the manuscript.

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CONFLICT OF INTEREST

The authors have nothing to disclose.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

CONSENT

Written informed consent was obtained from the patient and a legal guardian to publish this report in accordance with the journal's patient consent policy.

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