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Aortic dilation in Sotos syndrome: An underestimated feature?

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Sotos syndrome (OMIM #117550) is characterized by overgrowth (height and/or head circumference ≥2 *SD* above the mean), a distinctive facial appearance, and learning disability. While these three characteristics are considered cardinal signs of Sotos syndrome, additional major features may be present. These include: behavioral problems, advanced bone age, congenital heart defects, maternal pre-ecclampsia, neonatal hypotonia, renal anomalies, and epilepsy. Moreover, over 15% of patients with Sotos syndrome shows manifestations suggestive of connective tissue involvement, including joint hypermobility, scoliosis, and pes planus (Tatton-Brown et al., 2005).

Robertson and Bankier (1999) reported three patients diagnosed with Sotos syndrome on a clinical basis only, who showed marked connective tissue involvement, especially cutis laxa. Two of them exhibited mild diffuse dilation of the ascending aorta, a sign that had never been reported before in the literature as associated with Sotos syndrome. However, given the absence of molecular testing to confirm the diagnosis of Sotos syndrome, the hypothesis of a new phenotype, or of the co-existence of more conditions, could not be excluded.

Hood et al. (2016) reported the molecular confirmation of Sotos syndrome of the three patients previously reported by Robertson, and added a new individual showing the same clinical features. A 5-year follow-up documented the persistence and the stability of the mild but diffuse dilation in the two patients (PATIENT 1 and PATIENT

3, see Table 1) previously reported by Robertson (Robertson and Bankier, 1999), and it is stated that prophylactic beta blocker therapy was started on an empirical basis.

The authors proposed that marked connective tissue laxity could be part of Sotos syndrome, but raised concerns about management, as long-term natural history of aortic dilatation in Sotos syndrome is currently unknown.

The clinical evolution of ascending aortic aneurysms is indeed often related to their location and primary cause. For example, patients with bicuspid aortic valve or those affected by collagenopathies (Marfan, Loeys-Dietz syndrome, etc.) present with a more rapid expansion rate compared to isolated aortic dilation (Nataf and Lansac 2006). Generally dilation of the ascending aorta requires particular care in the identification of the critical size at which risk of rupture or dissection becomes greater than the risk of elective surgery.

Cardiovascular signs previously reported in Sotos syndrome are essentially congenital heart defects, as septal defects, patent ductus arteriosus, pulmonary stenosis, etc. (Leventopoulos et al., 2009). Therefore, indication to and timing of periodical ultrasound evaluation to date is related to the presence of signs or symptoms of heart disease. In the case of increased risk of developing aortic dilation, however, cardiologic follow-up should be recommended in all Sotos patients.

TABLE 1 Clinical and genetic features of Sotos patients with aortic dilation

Patients	Cases of the present report					Hood et al., 2016			Foster et al., 2019			
	P1	P2	P3	P4	P5	I	III	IV	COG1878	COG1918	COG2057	COG1879[a]
NSD1 variants	Exon 7c.3958C > T p.(Arg1320*)	Exon 5c.2386_2389del p.(Glu796Ilefs*10)	Exon 5c.2954_2955del p.(Ser985Cysfs*25)	Exon 5c.1527del p.(Ser510Valfs*2)	Exon 8c.4217_4220delp. (Arg1406Asnfs*12)	Exon 5c.2894C > G p.(Ser965*)	Intron 7c.4192 + 1G > A p.(Val1308Glufs*21)	Exon 5c.3618_3619insGAGTT p.(Arg1207Glufs*14)	Exon 18c.5768_5769del p.(Thr1923Serfs*22)	Exon 20c.6070C > T p.(Gln2024*)	Intron 20c.6152-5 T > G p.?	Exon 23c.6483G > A p.(Trp2161*)
Sex	F	M	M	M	M	M	M	n.a.	M	F	F	F
Current age (y)	9	7	18	9	8	38	32	1.5	35	22	48	46
Weight SDS	0.86	0.24	−0.74	1.54	0.79	−0.38	2.11	n.a.	2.2	0.1	n.a.	3.7
Height SDS	2.7	0.68	0.92	2.69	1.81	0.29	0.81	n.a.	0.8	1	−0.1	6
OFC SDS	3.08	3.49	1.75	3.53	2.38	3.78	2.29	n.a.	3.9	1.1	0.8	6.1
Aortic dilation pathological Z-scores	STJ: 2.50 AscA: 2.50	STJ: 2.33	AA: 3.47 AB: 3.37 STJ: 3.23 AscA: 3.28	STJ: 2.60	AB: 2.14 STJ: 2.81 AscA: 3.79 DS: 5.25	n.a. Diffuse dilatation of the AscA	n.a. Mild diffuse dilatation of the AscA	n.a. Mildly dilated aortic root, moderately dilated AscA	n.a. Mild aortic root dilatation	n.a. Mild aortic root dilatation	n.a. Borderline aortic sinus dilation	n.a. Borderline aortic dilatation
Age at diagnosis of aortic dilation	9 y	7 y	<1 y	9 y	<1 y	n.a.	15 y	17 m	n.a., But appeared to resolve	n.a., But appeared to resolve	47 y	n.a.
Congenital heart defects	ASD, PDA	/	ASD	/	/	/	/	/	/	/	/	/
Other connective tissue involvement signs	Scoliosis	/	Joint hypermobility, vesicoureteric reflux,	Pes planus	Joint hypermobility	Redundant skin, joint hypermobility	Redundant skin, joint permobility, pes planus, megacystis, hydroureters, hydronephrosis, inguinal hernia, gastro-esophageal reflux, redundant duodenal mucosal folds	Redundant skin, joint hypermobility, hydronephrosis	Scoliosis	Kyphoscoliosis	Scoliosis	Scoliosis

Abbreviations: SDS, standard deviation score; OFC, occipitofrontal circumference; AA, aortic annulus; AB, aortic bulb; STJ, sinotubular junction; AscA, ascending aorta; DS, distal segment (more of 3 cm from annulus); n.a., not available; y, years; m, months, ASD, atrial septal defect; PDA, patent ductus arteriosus.

aPatient COG1879 was not reported in the text, but was signed as borderline aortic dilation in supplementary table S1 (Foster et al., 2019).

Furthermore, a recent important review about the adult phenotype in Sotos syndrome reported four new cases of aortic dilation, two of which appeared to have resolved spontaneously in adulthood (Foster et al., 2019; Table 1). Unfortunately, no focused echocardiograms were performed in all 44 adult patients, preventing from knowing the prevalence of aortic dilatation in adulthood.

In order to investigate the real prevalence of thoracic aortic dilation in Sotos syndrome, in the context of scheduled clinical checks we then performed focused echocardiograms with aortic root and ascending aorta Z-score measurement in 29 Italian molecularly confirmed Sotos patients aged 3–18 years old.

In our study aortic dilation was detected in five out of 29 (17%) affected individuals (Table 1).

In three patients (P1, P2, and P4), we detected a mild dilation that mainly involved the sinotubular (ST) junction for the first time, and only periodic follow-up will be able to assess for progression. In the other two patients (P3 and P5) aortic dilatation was already known from early infancy, and cardiac follow-up of, respectively, 17 and 7 years was available.

P3 is an 18-year-old male. At 12 months of age, he underwent surgical repair of *ostium secundum* atrioventricular defect, and aortic bulb dilation was detected (Z-score 3.00) that remains substantially stable at yearly follow-up. When he was 17-year-old cardiac MR was performed (Figure 1), which ascertained a slight dilation of the aortic bulb (Z-score 3.5) and proximal ascending aorta (Z-score 3.00), which was confirmed on ultrasound at 18 years of age (Figure 1 and Table 1).

P5 is a 9-year-old male. The first diagnosis of aortic dilation was made during a screening echocardiography, at the age of 1 year. The exam showed patent ductus arteriosus (PDA) and dilatation of the aortic diameters: anulus 12 mm (Z-score 0.78), sinuses 19 mm (Z-score 2.60), ST junction 17 mm (Z-score 3.18), ascending aorta 18 mm (Z-score 3.48). With the clinical suspicion of Marfan or Loeys-Dietz Syndrome, as reported in the literature, he was started on Losartan until age 4 years when we observed no more progressive dilatation of the aorta diameters. Angio-CT was performed 1 year after the beginning of prophylactic therapy, confirming echocardiographic findings, and showing proximal supra-aortic trunks longer than normal, expansion of the pulmonary artery common trunks, and dilatation of the
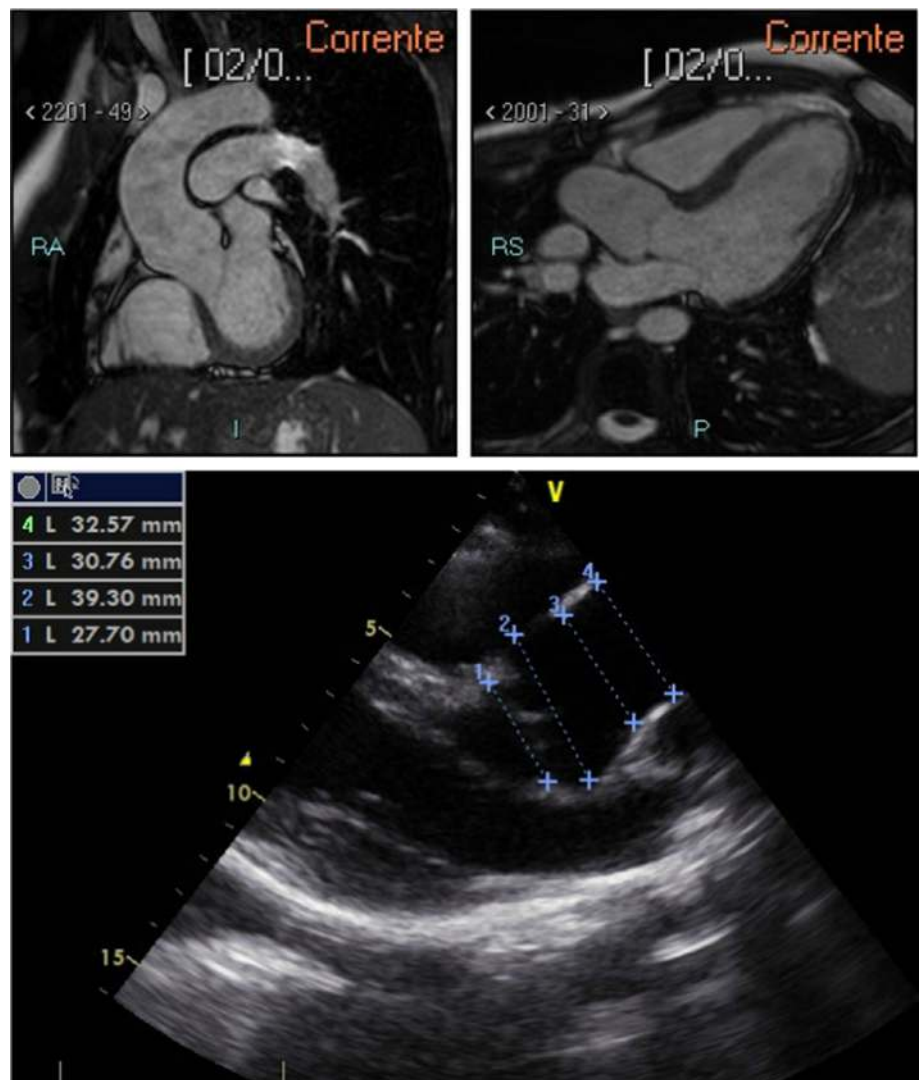

FIGURE 1 Patient P3: Heart magnetic resonance performed when he was 17-year-old, and ultrasound evaluations, documented a slight dilation of aortic bulb and proximal ascending aorta [Color figure can be viewed at wileyonlinelibrary.com]

aortic sinuses (diameter 19 mm) and of the aortic valve, with arterial tortuosity of the internal carotid.

Karyotype and array-CGH were negative, as well as molecular investigations for Loeys-Dietz (*TGFBR1*, *TGFBR2*) and Marfan (*FBN1*) syndromes. Conversely, Sotos syndrome was suspected due to other clinical manifestations, namely overgrowth and dysmorphic features, and targeted molecular test showed a de novo *NSD1* (OMIM*606681) pathogenic variant that confirmed the diagnosis of Sotos syndrome. The last cardiac evaluation at 9 years of age showed stability of the sizes of proximal aorta, but a dilatation on the distal segment (>3 cm from the annulus) with a maximum diameter of 32 mm (Z-score 5.25) was noted (Figure 2). Re-introduction of Losartan therapy was hypothesized, although no information about the effectiveness of prophylactic therapy in this condition is available.

Both P3 and P5 patients showed joint hyperlaxity, and one of them had severe bilateral vesicoureteral reflux that needed surgery at 4 years of age, but none of our patients exhibited redundant skin.

In our study, we report on five new cases of aortic dilation, supporting the hypothesis that this abnormality could be underestimated in Sotos syndrome. In three patients (P1, P2, and P4) indeed a mild aortic involvement was firstly detected by our focused study. Of note, P1 and P4 performed cardiac follow-up in the first years of life due to congenital heart defects (see Table 1), but no aortic dilation was detected, highlighting that a normal echo in infancy is not sufficient to exclude the possible development of a dilation later in life.

On the other hand, none of our five patients showed redundant skin, and only one of them had vesicoureteral reflux. We therefore hypothesize that the grade of general connective tissue involvement may not be indicative of an increased risk of developing aortic dilation.
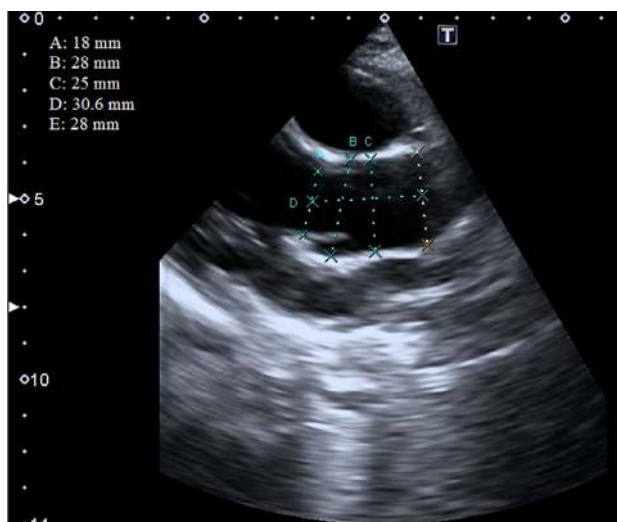

FIGURE 2 Patient P5: Cardiac ultrasound evaluations showed dilation of proximal aorta (bulb, ST junction, and ascending aorta); at last evaluation, a dilatation of the distal segment (>3 cm from annulus) with maximum diameter 32 mm (Z-score 5.25) was also noted [Color figure can be viewed at wileyonlinelibrary.com]

As previously stated by Hood and colleagues, our report confirms the apparent absence of a genotype–phenotype correlation for aortic dilation development in Sotos syndrome.

Maves et al. (2007) stated that, due to distinctive facial gestalt, tall stature, joint hypermobility, and lack of awareness of the disease among adult medicine physicians, a potential referring diagnosis for adult Sotos patients could be "possible Marfan syndrome" (Maves et al., 2007). In the first years of life a collagenopathy was actually suspected also in P5, due to his cardiovascular features. Similarly, SNP array, Sanger sequencing of the *TGFBR1* and *TGFBR2* genes, and subsequent Whole Exome Sequencing analysis had been performed in Patient 3 by Hood et al. (2016), with no detection of pathogenic variants in other genes.

Therefore, the confirmation that dilation of the thoracic aorta is a possible and likely underestimated sign of Sotos syndrome makes this condition even more similar to collagenopathies, although the prognosis seems to be better, as no cases of acute morbidity or mortality related to aortic dilatation in Sotos patients have been reported until now (Foster et al., 2019). Of note, generally no data about late adulthood (>50 years) clinical problems (Foster et al., 2019) and cause of death in Sotos syndrome are available to date.

Dilatation and aneurysms are due to deterioration and consequent weakening of the arterial walls. It is known that thoracic aorta aneurysms (TAA) can be caused by mutations directly influencing the extracellular matrix (ECM) components of arterial walls (i.e., *FB1* encoding fibrillin 1, *ELN* encoding elastin; Szabo et al., 2006), elastogenesis and collagen metabolism (e.g., *EFEMP2*; Dasouki et al., 2007), smooth muscle contraction apparatus (e.g., *ACTA2*; Guo et al., 2007), or by mutations of genes encoding various members of the transforming growth factor β (TGF-β) signaling cascade (Loeys et al., 2005). Moreover, new insights into the pathogenesis of TAA have recently focused on epigenetic regulation of gene expression, including the role of histone methylation and acetylation, deoxyribonucleic acid methylation, and noncoding ribonucleic acids (Boileau et al., 2018; Kim and Stansfield 2017; Shah et al., 2015). Epigenomics represents a crucial link between genomic and phenotypic expression that depends on both underlying genetic and environmental factors. Of note, the causal gene of Sotos syndrome, *NSD1*, is known to encode a histone methyltransferase involved in chromatin regulation, whose epigenetic effects cause the clinical features (Fahrner and Bjornsson 2014). Although no known direct link between *NSD1* variants and the development of aortic dilation has been found yet, a possible epigenetic correlation can be hypothesized.

Differential diagnosis between Sotos syndrome and the cited collagenopathies, that could be complicated by high stature and possible similar connective tissue involvement, is however often possible thanks to dysmorphisms evaluation and the detection of other features that could orient to the different conditions. For example, the presence of lens dislocation, pectus excavatum or carinatum and arachnodactyly could orient to Marfan syndrome or Loeys Dietz syndrome in the presence of arterial tortuosity, while if macrocephaly, intellectual disability, epilepsy, advanced bone age, or cardiac/renal malformations are detectable, Sotos syndrome diagnosis is suggested.

In conclusion, we demonstrated that the prevalence of aortic dilatation in Sotos syndrome might be likely underestimated, as screening echocardiograms may not be routinely performed in Sotos patients in the absence of cardiac signs or symptoms. Although in the reported patients (Foster et al., 2019; Hood et al., 2016) the aortic dilatation seems non-progressive, one of our pediatric patients showed slow but progressive dilation now requiring prophylactic medical therapy.

Cardiac screening and management recommendations in Sotos syndrome remain challenging. However, in order to better characterize the long-term natural history and the true prevalence of thoracic aortic dilatation in individuals with Sotos syndrome, we propose that periodical echocardiograms should be recommended. Further literature reports, especially of adult patients, are needed to confirm our observation.

In the meanwhile we suggest to perform ultrasound checks every 2–3 years in childhood and every 3–5 years in adulthood in the presence of normal aortic sizes; annually or as clinically indicated if a dilation has been detected.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

L.P., L.M., and D.M. were involved in conception and design of the study, L.P. wrote the manuscript, L.M. performed all the focused echocardiograms, A.C.C., A.R., A.S., A.P. were involved in patients' evaluations. D.M., A.C., P.G.M., D.C., and M.G. revised the manuscript and made substantial scientific contributions. All authors read and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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