Arterial tortuosity in pediatric Loeys-Dietz syndrome patients

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ABSTRACT

Introduction

Loeys-Dietz syndrome (LDS) is an autosomal connective tissue disorder commonly presenting with hypertelorism, bifid uvula, aortic aneurysms and arterial tortuosity. The aim of the present study was to investigate differences in tortuosity index (TI) between genotypes of LDS, possible progression over time and its use as an adjunctive prognostic tool alongside aortic dimensions to aid timely surgical planning in paediatric patients.

Methods

A retrospective observational study of paediatric LDS patients referred to our centre (November 2012-February 2021) was conducted. Using magnetic resonance angiography (MRA) with 3D maximum intensity projection volume-rendered angiogram, arterial TI was measured.

Results

23 patients had genetically confirmed LDS with at least one head and neck MRA and 19 had no less than one follow-up MRA available. All patients presented arterial tortuosity. Patients with *TGFBR2* variants had greater values of TI compared to patients with *TGFB2* variants (P=0.041).

For patients who did not undergo surgery (n=18), z-scores at the level of the sinus of Valsalva showed a significant correlation with vertebral TI (r_s=0.547). There was one death during follow-up.

Conclusion

This study demonstrates that patients with LDS and *TGFBR2* variants have greater values of TI than patients with *TGFB2* variants and that greatest values of TI are associated with increased aortic root z-scores. Furthermore, as TI decreases over time, less frequent neuroimaging follow-up can be considered. Nevertheless, additional studies are needed to better define more accurate risk stratification and long-term surveillance in these patients.

Keywords

Loeys-Dietz Syndrome

Arterial Tortuosity

Aortic dilatation

Paediatric population

Magnetic Resonance Angiography

Computed Tomography Angiography

INTRODUCTION

Loeys-Dietz syndrome (LDS) is an autosomal connective tissue disorder commonly presenting with hypertelorism, bifid or broad uvula or cleft palatae, aortic aneurysms and generalized arterial tortuosity (1)(2). LDS is caused by variants in the transforming growth factor β (TGFβ) receptor I (*TGFBR1*) and II (*TGFBR2*) genes, in the mothers against decapentaplegic homolog 2 (*SMAD2*) and 3 (*SMAD3*) genes, and in the transforming growth factor β 2 (*TGFB2*) and 3 ligand (*TGFB3*) genes (2)(3)(4).

LDS has been associated with vascular anomalies with an increased risk of neurovascular pathology such as intracranial aneurysms (5). Arterial tortuosity has been reported in 80-100% of LDS patients and is generally most prominent in the carotid and vertebrobasilar system (5)(6)(7). Current adult guidelines include head to pelvis magnetic resonance angiography (MRA) or computed tomography angiography (CTA) at the time of diagnosis of LDS to assess for arterial aneurysms and tortuosity and to repeat imaging on a yearly basis (8). Nevertheless, paediatric guidelines are lacking with respect to surveillance. Moreover, there is scarce data regarding potential associations between the extent of cerebrovascular tortuosity and its use as a prognostic marker for elective surgery before adverse cardiovascular outcomes namely aneurysm, dissection or even death occur (5). Hence, the aim of this study was to evaluate these associations.

Met opmerkingen [BL1]: This looks strange, normally with endnote it would be (5-7)

MATERIALS AND METHODS

Data collection

A retrospective observational study was conducted of paediatric individuals (aged ≤18 years) with a diagnosis of LDS referred to Great Ormond Street Hospital between

November 2012 and February 2021. The study was approved by the Research Board and consent waived in view of the retrospective data collection. Electronic patient records were systematically reviewed.

Clinical evaluation

LDS diagnosis was determined by the presence of clinical characteristics of LDS (craniofacial features, aortic dilatation and/or tortuosity) alongside a documented TGFβ variant (5). All patients underwent clinical evaluation including personal and family medical history, physical examination, resting 12-lead ECG, echocardiography, cardiac magnetic resonance imaging (MRI) and MRA of the head and neck.

Study population

Patients that had a confirmed LDS diagnosis and had undergone at least one cardiac MRI and a head and neck MRA were retrospectively reviewed.

Genetic testing

A thorough clinical evaluation by a medical geneticist specialized in the diagnosis of connective tissue disorders was performed in patients with clinically suspected LDS. In all patients, a subsequent diagnostic genetic panel including genes associated with heritable aortopathies was sent.

Magnetic Resonance Angiography analysis and tortuosity index

MRA studies were performed using a 1.5-Tesla or 3 Tesla Siemens scanner with a suitable coil for each patient size. In patients <6 years of age, the study was performed

under general anaesthesia or deep sedation as they could not cooperate with the procedure.

The initial and the most recent follow-up MRA scans, if available, were collected from each patient's electronic medical records. They were analysed by a blinded single investigator. Using a free and open source software application for medical image computing (3D Slicer) (6), a 3D volume-rendered angiogram model was generated from the source gadolinium-enhanced MRA for each patient for both the initial and the most recent MRA separately (Figure 1) (9). The software allows a user to rotate the 3D volume-rendered data set in any arbitrary direction in order to obtain a more accurate measurement of tortuosity and simultaneously plot a path that follows the tortuous vessel in 3D space (5). The patient's head and neck vessels needed to be segmented from the MRA images, were subsequently uploaded onto the database of 3D Slicer in order to create a 3D volume rendered model. It allowed to select arterial tissue and make a robust separation of the vessels, distinguishing arterial tissue from bone and providing a preliminary 3D segment. Unnecessary fragments and artefacts were removed. The final 3D segmentation was exported as a 3D model node to carry out the centre-line and straight-line measurements (Figure 1A). These 3D volume rendered models allowed accurate measurements of both internal carotid and vertebral arteries alongside petrous segments of the carotid artery. The internal carotid and vertebral arteries were measured bilaterally to determine the arterial tortuosity index (TI) which was used to quantify the excess vessel length using the previously reported distance factor: [(centre-line length/straight-line length) − 1] x 100 (Figure 1B) (5)(6). Centre-line and straight-line distances of each vertebral artery were measured from the origin of the vessel to a point before the normal bend of the vertebral artery at the level of C2 (10). Each patient was assigned with the TI of the most tortuous vertebral artery.

The interval percentage change in TI over time was measured for each patient with follow-up MRA. It was calculated by subtracting the initial raw score TI from the most recent raw score TI and dividing by the initial raw score and then multiplied by 100: (initial TI – recent TI/initial TI) x 100. A vertebral artery TI of 0-10 was used as the normal reference range as previously reported (6). The petrous carotid artery was measured bilaterally for horizontal elongation using linear measurements. When analysing the data with regards to genetic variants and association to tortuosity, the greatest TI between the right and left arteries was selected for comparison.

Magnetic Resonance Imaging analysis and aortic measurements

Cardiac MRI images were blindly analysed by an experienced investigator according to current guidelines (11)(12). Aortic diameters were standardised to account for body height and weight and presented as aortic z-score values (12). The most recent aortic diameter (millimetres) and z-score or the latest measurements prior to surgery (when applicable) were obtained for each patient.

Statistics

Data were explored for normality by a Kolmogorov-Smirnov test/Saphira-Wilson and further analysed as appropriate. Normally distributed data are presented as mean values (± standard deviation) and non-normally distributed variables as a median [interquartile range (IQR)]. Categorical variables are expressed as number (n) and percentages (%). Spearman rank correlation coefficient (rS), Student's t-test, Friedman and Kruskal-Wallis test were used when appropriate to compare continuous variables. Post Hoc Wilcoxon signed-rank tests using Benferroni adjustment were also applied when appropriate. We performed receiver operating characteristics (ROC) curve analysis for

vertebral TI and cardiac surgery. A P-value <0.05 was considered to be statistically significant for all data. Statistical analysis was performed using Statistical Package of Social Sciences (SPSS, version 28.0, IBM inc, Chicago, Illinois).

RESULTS

We identified 43 patients at our centre institution with confirmed LDS diagnosis. The final study cohort consisted of 23 patients (53.5%) who underwent one neurovascular MRA and one cardiac MRI at the minimum. Among them, 19 patients (82.6%) underwent at least one follow-up head and neck MRA although it was available for analysis in 16 (69.5%). Table 1 shows baseline characteristics of LDS patients.

Cerebral imaging analysis and arterial tortuosity

All patients in our cohort had arterial tortuosity when using a cut off of 10 (Figure 2A). Table 2 includes the arterial tortuosity for bilateral vertebral and internal carotid arteries from our LDS cohort.

There were no significant differences in tortuosity between the right (RICA) and left internal carotid artery (LICA) (P=0.563). However, there was a statistically significant difference in tortuosity between the right (RVA) and left vertebral arteries (LVA), the RVA and RICA, the RVA and LICA, the LVA and RICA, and the LVA and LICA (P=0.024, P=<0.001, P=<0.001 P=0.003 and P<0.001, respectively).

Considering the greatest TI score out of the RVA and LVA for each patient at the time of the first head and neck MRA, 91.3% of the patients (n=21) had increased vertebral artery tortuosity (TI>10). The follow-up head and neck MRA was available in 16 patients (69.6%). Of those, 100% had increased vertebral artery tortuosity.

Supplementary table 1 shows interval of change in TI for bilateral vertebral and internal carotid arteries. There was no statistically significant difference between the interval changes in TI in the aforementioned arteries [$\chi^2(3)=1.275$, p=0.735]. However, there was a significant difference between the interval change in TI for both the right and left petrous carotid artery: [t(14)=3.083, *P*=0.008] and [t(14)=2.731, *P*=0.016], respectively. In our cohort, no patients were found to have aneurysms nor other vascular anomalies or intracranial lesions.

Genetic variants

There was a statistically significant difference between median TI in the RICA, LICA and ICA in patients with the *TGFBR2* variant (28.3 [18.5 – 36.6], 28.2 [20.9 – 41.7] and 34.0 [25.9 – 47.8], respectively) compared with the remaining genetic variants (11.6 [8.0 – 22.4], 12.5 [5.6 – 16.7] and 14.3 [8.5 – 25.0]) (*P*=0.014, *P*=0.003 and *P*=0.003, respectively). There was no significant difference between median TI in RVA, LVA or VA in patients with the *TGFBR2* variant with respect to the rest of genetic variants (*P*=0.065, *P*=0.056 and *P*=0.056, respectively). Figure 3 depicts the box plots of TI by genetic variants.

Cardiac outcomes and follow-up

5 patients (21.7%) underwent a total of 6 cardiac surgical interventions with a median age of 13 [10.3-17.3] years: aortic root replacement with valve sparing technique (n=2; 40%), Bentall procedure (n=2, 40%), and personalized external aortic root support (PEARS) and coartectomy surgery (n=1, 20%) (Supplementary Table 2). The median z-score at the level of the sinus of Valsalva before surgery was +7.5 [7.2-8.3].

In our cohort, using the initial TI scores and carrying out ROC analysis for vertebral TI and cardiac surgery, a vertebral TI of 50 provided a sensitivity of 80% and a specificity of 67% as a predictive threshold for cardiac surgery (Figure 4).

Regarding the 18 patients (78.3%) that did not undergo surgery, the median z-score was 4.5 [2.9-6.4] with increasing z-scores showing a significant correlation with vertebral TI (r_S=0.547, P<0.001). On analysis of the annual change of the z-score at the level of the sinus of Valsalva among unoperated patients, the median change per year was 0.5 [0.2-0.5]. No correlation was found with annual change in z-score and vertebral TI.

There was one death (4.3%) over follow-up. This patient underwent a Bentall procedure 2 months earlier and was subsequently on anticoagulant therapy. He suddenly died at the age of 19 years, with no available data on death circumstances and no post-mortem examination performed.

DISCUSSION

This study reports the arterial tortuosity analysis of the head and neck vessels of an exclusively LDS paediatric cohort by producing 3D volume rendered models of MRA images. We noted that patients with *TGFBR2* variants have greater values of TI in vertebral and internal carotid arteries than patients with *TGFB2* variants. Furthermore, we demonstrated that greatest values of TI were associated with higher aortic root z-scores.

Arterial tortuosity and intracranial pathology

In line with previous studies, 100% of our patients presented arterial tortuosity (5)(6)(7). Furthermore, our results showed stability or even a decrease of the head and neck arterial tortuosity among paediatric LDS. In line with Lo Presti et al, while there was a significant difference between the interval change in TI for petrous carotid arteries, there was no statistical difference between the interval changes in tortuosity in vertebral and internal carotid arteries in our cohort. Nevertheless, there was a trend towards improvement in tortuosity during follow-up in these latter arteries (5). This subjective amelioration could be attributed to the young age of our patients implying that their necks elongated over time as they aged and grew in height, thus diminishing the degree of arterial tortuosity over surveillance (5). This lack of progression in tortuosity raises the question of which is the most appropriate time frame for follow-up imaging of younger patients with LDS in order to minimise risks associated with MRA and maximise clinical benefit. In this context, LoPresti et al recently described a low rate of TI progression among their LDS cohort highlighting the need to determine patients that require a closer follow-up to lessen avoidable screening and exposure to anesthesia, contrast and radiation (5). The present study further strengthens the suggested screening recommendations by LoPresti et al that LDS patients without high-risk characteristics, aneurysms nor artery tortuosity on first or consecutive follow-up imaging, can be monitored safely with less frequent neuroimaging (5).
Specifically, LoPresti et al suggested an initial neurovascular image either by MRA or CTA during the first year of diagnosis with neurovascular imaging surveillance in patients ≤25 years depending on the findings of the first neurovascular imaging: in 6 months and referral to neurosurgery in the setting of an intracranial aneurysm, in 2 years if arterial tortuosity is present and in 5 years in the absence of neurovascular pathology (5).

Met opmerkingen [LB2]: Looks strange

As aforementioned, surveillance of arterial tortuosity is required as development of intracranial aneurysm has been reported (14)(15). Precisely, LoPresti et al described an incidence of intracranial aneurysms of 5.1% in their LDS cohort (5). Additionally, intracranial haemorrhage has been reported as the third cause of mortality in LDS patients due to intracranial aneurysms rupture (5)(7). Nevertheless, in our cohort, no patients presented aneurysms nor other vascular lesions.

Genetic variants

In our study population, patients with *TGFBR2* variants had statistically significant greater values of TI in the RICA, LICA and ICA compared to patients with the remaining genetic variants. Morris et al reported a trend towards a greater vertebral TI among patients with *TGFBR2* variants in comparison with patients with *TGFBR1* variants, although this difference was not statistically significant, likewise our results (6). Our greater values of TI in these arteries could be related to the fact that patients with *TGFBR2* variants have more severe phenotype of LDS (5)(6). Precisely, Tran-Fadulu et al demonstrated that patients with *TGFBR2* variants were more likely to have dissections at lower aortic diameters than patients with *TGFBR1* variants (17). It could be speculated that different genetic variants affect the level of TGF-β activation to varying extents which may be reflected in the degree of arterial tortuosity or different cardiovascular risk.

Cardiac outcomes

Using the initial TI scores and carrying out ROC analysis for vertebral TI and cardiac surgery, we found that a vertebral TI of 50 provides a sensitivity of 80% and a specificity of 67% as a predictive threshold for cardiac surgery. Moreover, we found a significant correlation between vertebral TI and aortic root z-score. This concurs with Morris et al. who demonstrated that higher vertebral TI in patients with LDS was associated with greater adverse outcomes, namely increased rate of cardiac surgery, more significantly dilated aortic root, and a younger age at dissection, cardiac

intervention and death (6). Specifically, they noted that a higher TI was associated with a younger age at surgery (6). Earlier age at dissection and death was associated with vertebral TI ≥50 respect to TI <50 (P=0.001 versus P<0.001) (6). It could be hypothesized that vertebral TI alongside aortic root z-score can be used as a measure of vascular fragility and a prognostic tool.

Even though the real correlation between vertebral arterial tortuosity and cardiac outcome is elusive, it has been speculated that arterial tortuosity, dilatation and dissection of vessels are a manifestation of arterial wall fragility in patients with LDS caused by abnormalities in the TGF-β signaling pathway which leads to a disturbance in the elastic fibers and subsequent weakening of the wall of the vessels (13)(18).

LIMITATIONS

The study is limited by the small cohort of patients which not only limits the comparison between LDS patients with different genetic variants but also the power of the statistical analysis. The present trial is limited by its retrospective design with intrinsic limitations that could lead to inherent ascertainment bias, mainly in that consensus guidelines for and timing of MRA have not been reported. Therefore, in our study, they were not standardized.

Furthermore, the follow-up periods between MRAs are erratic. Hence, interval changes in vertebral TI are variable. Consequently, they could not be compared between subgroups. Moreover, as 3D reconstruction requires many steps of post-processing, there could be loss and misinformation; however, the consistency within the study was maintained as a repeated technique and a standard protocol was followed for each measurement.

CONCLUSION

This study demonstrates that patients with LDS and *TGFBR2* variants have greater values of TI in vertebral and internal carotid arteries than patients with *TGFB2* variants. Besides, it shows that greatest values of TI are associated with increased aortic root z-scores. Furthermore, it strengthens the previously suggested surveillance of LDS patients without high-risk characteristics, aneurysms or artery tortuosity with less frequent neuroimaging. Nevertheless, additional studies with larger cohorts and further long-term prospective follow-up are required in order to define more accurate risk stratification and long-term surveillance of arterial tortuosity in LDS patients.

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Table 1. Demographic characteristics of paediatric Loeys-Dietz syndrome cohort.

Baseline information	**Total cohort (n = 23)**
Female, n (%)	6 (26.1)
De novo genetic variant, n (%)	12 (52.2)
LDS genetic variant, n (%)	
TGβR 1, n (%)	4 (17.4)
TGβR 2, n (%)	12 (52.2)
SMAD3, n (%)	3 (13.0)
TGFβ2, n (%)	3 (13.0)
TGFβ3, n (%)	1 (4.3)
Age at the time of first available cerebral MRA, years [IQR]	10.3 [6.5-12.9]
Patients with an available follow-up MRA, n (%)	16 (69.6)
Follow-up MRA from first MRA, years [IQR]	3.0 [2.0-4.3]
Aortic surgery, n (%)	5 (21.7)
Deaths, n (%)	1 (4.3)

IQR: Interquartile Range; LDS: Loeys-Dietz syndrome; MRA: Magnetic Resonance Angiography

Table 2. Bilateral vertebral and internal carotid artery tortuosity indexes.

Arterial tortuosity index	Total cohort (n = 23)
Right vertebral artery, [IQR]	39 [20.2 – 84.9]
Left vertebral artery, [IQR]	32.1 [13.4 – 78.9]
Right Internal carotid artery, [IQR]	22.4 [8.5 – 29.6]
Left Internal carotid artery, [IQR]	17.5 [9.9 – 31.6]

IQR: Interquartile Range; LDS: Loeys-Dietz syndrome; MRA: Magnetic Resonance Angiography.

Supplementary table 1. Bilateral vertebral and internal carotid artery tortuosity index change over time.

Interval change in arterial TI (%)	Total cohort (n = 16)
Right vertebral artery, [IQR]	-13.9 [-22.6 – 1]
Left vertebral artery, [IQR]	-14.7 [-28.1 – 4.4]
Right internal carotid artery, [IQR]	-20.9 [-38.1 – 5.5]
Left internal carotid artery, [IQR]	-20.9 [-46.7 – -6.1]

IQR: Interquartile Range; TI: tortuosity index.

Supplementary table 2. Aortic surgery in our paediatric Loeys -Dietz syndrome cohort.

LDS genetic variant	Aortic surgery
TGFBR1	Valve-sparing and aortic root replacement.
TGFBR1	Coarctation repair and PEARS procedure.
TGFBR2	Mechanical vale and aortic root replacement (Bentall procedure).
TGFBR2	Valve-sparing and aortic root replacement.
TGBR1	Mechanical vale and aortic root replacement (Bentall procedure).

LDS: Loeys -Dietz syndrome; PEARS: Personalised external aortic root support.

Figure 1. A. 3D volume rendered segmentation of the internal carotid and vertebral arteries in a patient with Loeys-Dietz syndrome, segmented using 3D Slicer open-source software. **B.** Measurement of the distance factor achieved using the vascular modelling toolkit module on 3D Slicer open-source software.

3D: 3-dimensional.

Figure 2. Examples of degrees of tortuosity in our Loeys-Dietz syndrome cohort. **A.** 8 years old patient with VTI of 9. **B.** 11 year old patient with VTI of 32. **C.** 9 years old patient with a VTI of 39. **D.** 12 years old patient with VTI of 114.

VTI: vertebral tortuosity index.

Figure 3. Box plots of tortuosity index arteries by genetic variants. A. Right vertebral artery; B. Left vertebral artery; C. Right internal carotid artery; D. Left internal carotid artery.

TI: Tortuosity index.

Figure 4. Receiver operating characteristics (ROC) curve for vertebral tortuosity index and cardiac surgery.