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分担研究報告書

ロイス・ディーツ症候群の診断・治療のガイドライン作成および新規治療法の開発に向けた臨床所見の収集と治療成績の検討

分担研究課題：
ロイス・ディーツ症候群に伴った脊柱側弯症の手術加療-第二報

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研究要旨

ロイス・ディーツ症候群に合併した側弯症に対し、手術加療した4例の術後経過について報告する。手術時年齢は平均7.3歳、主弯曲Cobb角は平均103.5度。手術方法はgrowing rod法（2例）および後方矯正固定（2例）を施行した。合併症はインプラントの逸脱、創感染、偽関節のいずれかを全例に認めた。手術加療の際にはインプラントの脱転や術後感染の発症する可能性、心血管系の異常について十分に留意する必要である。

A．研究目的

ロイス・ディーツ症候群はMarfan症候群様の外見に頭蓋骨早期癒合症を合併する全身の結合織疾患であり、側弯症は本症に合併することは知られている[1]。平成22年度の本研究報告において、ロイス・ディーツ症候群に合併した側弯症に対する手術加療例の詳細について報告したが、今回はそれらの症例の、特に術後経過に関し報告する。

B．研究方法

脊柱側弯症に対し手術加療を施行したロイス・ディーツ症候群4例（男児 2例、女児 2例）を対象とした。手術時年齢は平均7.3±4.4歳（3-12歳）、術後経過観察期間は平均6.3±1.7年であった。体格は症例１：98cm(1.5SD)、11.5Kg （-1.1SD)、症例２：107cm（1.6SD)、13Kg（-1.4SD)、症例３：146cm（1.6SD)、33Kg（-0.1SD)、症例４：164cm(1.9SD)、44Kg(0.1SD)で、全例るい痩体型であった。術前の主カーブの平均Cobb角は102.8±16.9度（78-116度）であった。症例１、２でgrowing rod法を、症例３、４で一期的な後方矯正固定術を施行した。これらの症例の初回手術後の経過について検討した。

C．研究結果

症例1

女児、手術時、3歳10ヶ月。進行性の脊柱変形に対しgrowing rod法を施行した。術後、近位端フックの脱転を4度認め、その都度、フックや椎弓根スクリューの再設置を行った。さらに、創部感染を2度認め、洗浄・デブリドマンにより沈静化しないため、最終的にロッドを抜去した。１０歳時（術後６年）に大動脈弁輪部拡張（AAE）の進行を認め、ARB（ロサルタン）の投与を開始した。現在、AAE進行は抑制されているが、進行を認めた場合は、グラフト置換を検討予定である。さらに、心房中隔欠損も併発しており、治療を予定している。

症例2

男児、手術時年齢４歳10ヶ月。進行性の側弯変形に対し、growing rod法を施行した。術後６ヶ月で創部感染を認め、脊椎インプラントの抜去を行った。感染沈静後の術後１年時、再び脊椎インプラントを設置したが、創部感染が再発したため、再び脊椎インプラントの抜去を行った。その後は装具療法で経過観察を行っていたが、11歳時に後方矯正固定術を行った。なお、11歳時（術後6年）にAAEの進行を認めたため、ARB（ロサルタン）を開始した。今後AAEの進行を認めた場合は、グラフト置換を検討予定。

症例３

女児、手術時年齢11歳。後方矯正固定術を行ったが、術後２年時に第3/4腰椎間の偽関節による脊柱変形の進行と強い腰痛を認めたため、骨移植術を行った。術後４年経過した現在、明らかな心大血管病変は認めないが、視力障害、呼吸器障害が進行している。

症例４

男児、手術時年齢12歳。後方矯正固定術を行った。術中、横突起の骨折を認めた。さらに術後5ヶ月に最頭側端のフックが脱転し、体幹バランスは不良となったため、再手術を行った。術後６年経過した現在、心血管系の異常は認めていない。

Ｄ．考察

本研究の結果より、本疾患の脊椎手術治療は、骨の脆弱性のため脊椎インプラントの脱転が危惧される。本疾患は全身の結合織疾患であり、骨は非常に脆弱であるため術中、術後の特にgrowing rod法を施行する際は、インプラント脱転のリスクが高いと考えられる。そのため、今後はまずフックおよび椎弓根スクリューの設置後、二期的にgrowing rodを用いた矯正手術を行うといった工夫が必要であると考えた。また、全例るい痩体型であるため、褥創を原因とした創部感染の危険性にも十分に留意する必要がある。

さらに、１０−１１歳時にAAEの進行を２例に認めた。そのため、心血管系の異常に関しても留意が必要であると考えられた。

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E. 結論

- Loeys-Dietz症候群に合併した側弯症に対する術後経過について報告した。
- 手術加療の際にはインプラントの脱転や術後感染の発症する可能性、長期的には心血管系の異常が生じる可能性があるため、十分な留意が必要である。

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H. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
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S. 9

LOEYS-DIETZ SYNDROME VS MARFAN SYNDROME: BROAD SPECTRA OF AORTIC/NON-AORTIC PHENOTYPES IN JAPANESE PATIENTS

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Objectives: Loeys-Dietz syndrome (LDS) is a systemic connective tissue disorder characterized by vascular and skeletal manifestations caused by mutations in *TGFBR1* or *TGFBR2*. Although characteristic craniofacial and arterial manifestations are helpful for diagnosis of LDS, there are many overlapping features between LDS and Marfan syndrome (MFS). We tried to reveal phenotypic differences between LDS and MFS. We also analyzed the genotype-phenotype correlations in LDS.

Methods: We analyzed the clinical details of 30 Japanese LDS patients with *TGFBR1* mutations (14 patients) and *TGFBR2* mutations (16 patients) and compared them with those of MFS.

Results: Compared with patients genetically diagnosed as MFS, LDS patients were physically less dolichostenomelic and more had ocular hypertelorism. Although Annuloaortic ectasia was observed in most of the LDS patients, 11% of those who had already experienced TAAD were free of AAE. Congenital retinal abnormalities and immunologic disorders were often observed in LDS patients. Dural ectasia was observed in both, but the ectatic pattern was different. Significant differences between patients with *TGFBR1* and those with *TGFBR2* mutations were observed in regard to age at diagnosis, cleft/uvula abnormalities, skeletal involvement, lung involvement, and fulfillment of Ghent MFS diagnostic criteria. LDS patients with *TGFBR2* mutations tended to have more skeletal involvement and be diagnosed at a younger age, often initially as MFS, while those with *TGFBR1* mutations had a greater chance to be diagnosed only when aortic symptoms were manifested.

Conclusions: Patients suspected of LDS should be carefully examined for specific features and be tested for *TGFBR1*/*TGFBR2* mutations.

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ORIGINAL ARTICLE

High prevalence of vertebral artery tortuosity of Loeys-Dietz syndrome in comparison with Marfan syndrome

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Abstract
Purpose. Loeys-Dietz syndrome (LDS) is a connective tissue disease caused by mutations in the genes encoding the transforming growth factor-β receptor (TGFBR). LDS is associated with aneurysms or dissections of the aorta similar to Marfan syndrome (MFS) as well as arterial tortuosity and aneurysms in the peripheral arteries. The purpose of this study was to evaluate the arterial diseases of LDS to differentiate it from MFS.
Materials and methods. A total of 10 LDS patients with an identified mutation in TGFBR (6 male, 4 female; mean age 36.3 years) and 20 MFS patients with an identified mutation in fibrilin-1 who were age- and sex-matched to the LDS subjects (12 male, 8 female; mean age 37.1 years) were reviewed. The prevalence of vertebral arterial tortuosity (VAT) and peripheral aneurysm (PAN) was studied using computed tomography angiography.
Results. In all, 9 of the 10 LDS patients had VAT, and five PANs were observed in 3 patients. In contrast, 8 (40%) of the MFS patients had VAT, and 1 patient had a PAN. LDS had a higher prevalence of VAT ($P = 0.017$) by Fisher's exact test.
Conclusion. The VAT was highly prevalent among LDS patients. Thus, the presence of VAT has the potential to differentiate LDS from MFS.

Key words Loeys-Dietz syndrome · Vertebral artery tortuosity · Peripheral aneurysm · Transforming growth factor-β receptor

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Introduction

Aortic dissection typically occurs in older patients with a peak incidence during the sixth decade, but 7.2% of cases occur in young subjects.[1] Aortic dissection in this subgroup is related to connective tissue diseases, such as Marfan syndrome (MFS), vascular Ehlers-Danlos syndrome, and Loeys-Dietz syndrome (LDS). LDS is a newly described phenotype caused by mutations in the genes encoding transforming growth factor-β receptor (TGFBR).[2–4] Clinical features of LDS include vascular disease, craniosynostosis, cleft palate/bifid uvula, hypertelorism, congenital heart defects, and mental retardation. Patients with LDS, similar to those with MFS, have an aneurysm or dissection of the ascending aorta and dilatation of the aortic root. In contrast to MFS, generalized arterial tortuosity and aneurysms of arteries have been noted in patients with LDS.[4] Aortic rupture and dissection can occur in LDS patients with aortic root diameters not considered at risk in MFS.[5]

The exact prevalence of LDS is unknown, and its characteristics are not familiar to radiologists. However, given the fact that LDS has recently been discovered,

many cases might not have been diagnosed yet. Because vascular pathology is more aggressive in LDS than in MFS, it is important to recognize the characteristics of this disorder and to diagnose it correctly.

The purpose of this study was to review radiological findings of the arterial diseases of LDS and to differentiate them from those found in MFS. Particular attention was given to computed tomography angiography (CTA), which is used quite frequently in the clinical setting.

Materials and methods

The study was approved by our institutional review board. Written informed consent to use the patients' clinical and imaging data was not required because it was a retrospective study.

A total of 10 LDS patients with an identified mutation in TGFBR (6 men, 4 women; mean age 36.3 years, range 20–54 years) were retrospectively reviewed. Causes of hospitalization were aortic root dilatation in four patients and aortic dissection in six. Among these 10 LDS patients, 9 (90%) were in a postoperative state (1 with aortic repair, 3 with valve replacement, 5 with both).

A group of 20 MFS patients with an identified mutation in fibrilin-1 (12 men, 8 women; mean age 37.1 years, range 20–56 years) were also reviewed. MFS patients who were age- and sex-matched to the LDS patients were selected randomly from our database. Causes of hospitalization were aortic root dilatation in 11 patients, aortic dissection in 8 patients, and mitral valve regurgitation in 1 patient. In all 17 MFS patients (85%) were in a postoperative state (3 with aortic repair, 7 with valve replacement, 7 with both).

All patients had had clinical examinations including a physical examination and laboratory data by a cardiovascular team. Initial and follow-up CTA was performed in a clinical setting as described below. All patients had undergone genetic analysis according to the method reported by Akutsu et al.[6]

CT protocol

The CT angiography was performed using a multislice CT scanner (16 or 64 slices) with an iodine contrast material injection of 1 ml/kg with an iodine content of 350 mg I/ml or 370 mg I/ml. Injection time varied from 30 to 40 s with a variable injection rate. A saline chaser of 25 ml with the same injection rate as the contrast material was applied with a dual-syringe power injector. The scan started when the density in the region of interest (ROI) positioned at the ascending artery increased 100 HU from a baseline value using an intermittent monitoring scan. The CT scan covered from the neck to the pubis. A field of view (FOV) of 320 or 400 mm was adopted according to the patient's body size. For three-dimensional (3D) reconstruction, a 1 or 2 mm slice thickness data set without slice gap was used. The data set was sent to a commercially available workstation and a CT image server.

Imaging analysis

All CT images were reviewed on a Picture Archiving and Communication System (PACS) viewer with an adjustable optimal widow setting and stack-view system. Reconstructed images, such as 3D volume rendering or multiplanar reconstruction, were also used if needed.

The prevalence of arterial diseases was studied in both LDS and MFS subjects. Peripheral aneurysm and peripheral idiopathic dissection in the abdominal aortic branches were evaluated. Tortuosity in the vertebral artery and the common carotid artery was also evaluated.

The presence of aneurysm and dissection was analyzed visually. The tortuosity was graded on a 3-point scale (Fig. 1): 0, the artery runs straight or with a mild curve; 1, the artery turns with multiple curves or a severe curve of 10 mm distance from the upper to the lower portion of a curve; and 2, the artery has a pigtail-like or corkscrew-like curve. After summing up each score for the right and left arteries, the score for patients varied from 0 to 4.

Statistical analysis

For the statistical analysis, JMP software (version 7.0; SAS Institute, Cary, NC, USA) was used. Continuous

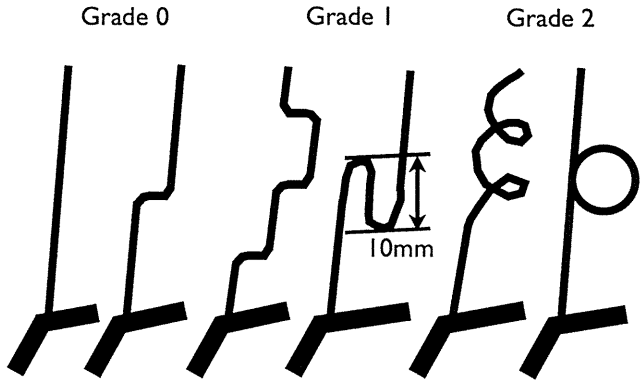

Fig. 1. Grading vertebral artery tortuosity. For grade 0, the artery runs straight or with a mild curve. For grade 1, the artery turns with multiple curves or has a severe curve, with 10 mm distance from the upper to the lower portion of a curve. For grade 2, the artery has a pigtail-like, or corkscrew-like, curve

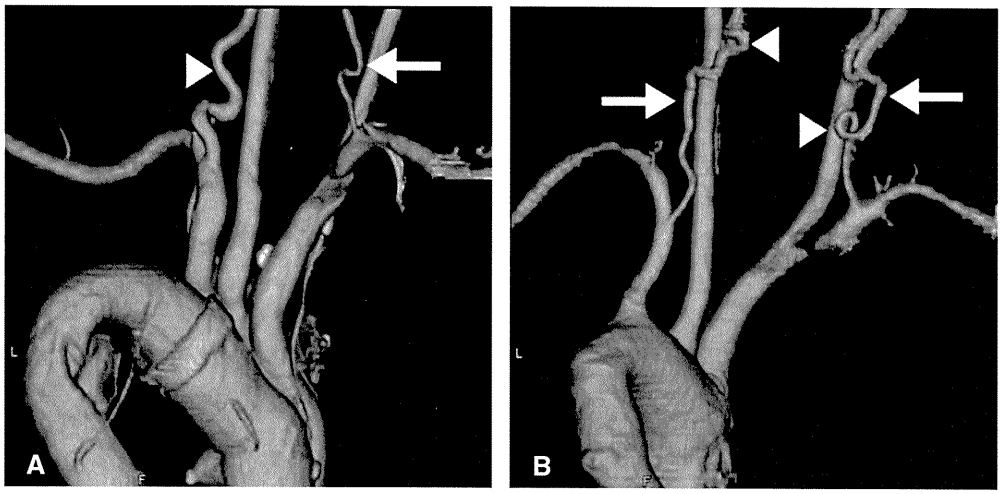

Fig. 2. **a** Computed tomography angiography (CTA) image, posterior view, of a 37-year-old patient with Loeys-Dietz syndrome (LDS). The patient is in a postoperative stage after aortic dissection. The right vertebral artery (*arrow*) is graded 0, and the left vertebral artery (*arrowhead*) as 1 because of its multiple curves. **b** CTA image from posterior view of a 19-year-old LDS patient. The patient underwent CT examination for preoperative evaluation of annuloaortic ectasia. Both vertebral arteries (*arrows*) are graded 2 owing to the pigtail-like curves (*arrowheads*). The right subclavian artery shows pseudostenosis owing to the artifact of contrast material in the vein

Table 1. Patient characteristics of Loeys-Dietz syndrome and Marfan syndrome

Characteristic	LDS	MFS	Difference
Gene mutation	TGFBR	FBN1	
No. of patients	10	20	
Age (years), mean ± SD	36.3 ± 12.6	37.1 ± 11.2	NS
Sex (M:F)	6:4	12:8	NS
Vascular disease:[a] (AAE/AD/other)	4/6/0	11/8/1	NS
Postoperative state	9 (90%)	17 (85%)	NS

AAE, annuloaortic ectasia; AD, aortic dissection; TGFBR, transforming growth factor-β receptor; FBN1, fibrilin-1; LDS, Loeys-Dietz syndrome; MFS, Marfan syndrome; NS, not significant using a significance level of $P < 0.05$

[a] Vascular disease that caused the patients' hospitalization

data were expressed as the mean ± SD. A two-tailed Student's *t*-test was used to compare continuous variables. The χ^2 test or Fisher's exact test was used for discrete variables. $P < 0.05$ was considered statistically significant.

Results

Patients' characteristics and vascular pathologies are summarized in Tables 1 and 2.

Arterial tortuosity

In all, nine (90%) of the LDS patients had vertebral arterial tortuosity (Fig. 2): two on the right side, three on the left, and four on both sides. Among the MFS patients,

Table 2. Vascular pathologies in Loeys-Dietz syndrome and Marfan syndrome

Characteristic	LDS	MFS	*P*
No. of patients	10	20	
Vertebral artery tortuosity			
Prevalence (no.)	9 (90%)	8 (40%)	0.017
Score[a]			
0	1	12	
1	3	4	
2	3	2	
3	1	2	
4	2	0	
Carotid artery tortuosity (no.)	0	0	NS
Peripheral aneurysm			
Abdominal branch	3 (30.0%)	1 (5.0%)	NS
Iliac artery	3 (33.3%)	3 (20.0%)	NS
Abdominal aortic aneurysm	1 (14.3%)	1 (8.3%)	NS

NS, not significant using a significance level of $P < 0.05$

[a] Score was calculated by the summation of both grades of vertebral arteries shown in Fig. 1

eight (40%) had vertebral artery tortuosity: two on the right side, two on the left, and four on both sides. The tortuosity scores are also noted in Table 2. The common carotid artery showed no tortuosity in any patients.

The LDS patients had a high prevalence of vertebral artery tortuosity ($P = 0.017$). The mean tortuosity score was 2.0 [95% confidence interval (CI) 1.26–2.73] for LDS patients and 0.7 (95% CI 0.18–1.22) for MFS patients.

Aortic and peripheral artery disease

A total of five peripheral aneurysms were observed in three LDS patients (30%). Three aneurysms presented in the hepatic artery, one in the superior mesenteric artery, and one in the pancreatic arcade. Three patients (33.3%) had common iliac artery aneurysms, and one (10%) had a common femoral artery aneurysm. Because one patient had iliac artery involvement secondary to aortic dissection, we excluded him from the analysis of iliac aneurysms. Among the seven patients without abdominal aortic dissection, an abdominal aortic aneurysm was observed in one patient (14.3%). No aneurysms were observed in the thoracic aorta and its branches. Because four patients had undergone thoracic aortic replacement, three of which were due to dissection, they were excluded from the analysis of the prevalence of aortic aneurysms.

Among the MFS patients, one (5%) had a hepatic artery aneurysm, and three (20%) had common iliac aneurysms. Among the 12 patients without abdominal aortic replacement, 1 (8.3%) had an abdominal aortic aneurysm. Because two patients had involvement of the celiac trunk and five of the iliac artery secondary to aortic dissection, such territories were excluded for evaluation of the prevalence of peripheral aneurysms. Because seven patients had thoracic aortic replacement and eight had abdominal aortic replacement, they were excluded from the analysis of the prevalence of aortic aneurysms.

The prevalence of peripheral aneurysms was not significantly different between LDS and MFS ($P = 0.057$).

Discussion

Our results showed that the high prevalence of vertebral artery tortuosity in LDS helps to differentiate LDS from MFS. Patients with LDS have aneurysms or dissection of the ascending aorta, similar to those observed in patients with MFS. In contrast to MFS, however, generalized arterial tortuosity and aneurysms of other arteries have been noted in patients with LDS.[4] On the other hand, there are some reports[7,8] that arterial tortuosity had not been found in their LDS groups although they had not been systematically evaluated in all patients. The exact prevalence of arterial tortuosity, especially in the vertebral artery, has not yet been reported. Our results showed that the vertebral arteries were highly affected in LDS patients.

Assessing the vertebral artery to help differentiate LDS from MFS is a superior method for a few reasons. First, the lower portion of the vertebral artery is easy to evaluate with thoracic or thoracoabdominal CTA. Second, the vertebral artery is rarely affected by aortic dissection, in contrast to the subclavian artery or carotid artery. Third, the vertebral artery is easy to evaluate because it runs straight, especially in young subjects. According to our unpublished data, among 10 subjects without either LDS or MFS (five men, five women; mean age 26.7 years), tortuosity was not observed in the vertebral artery. Arteries other than the vertebral artery (e.g., abdominal visceral arteries, iliac arteries) are difficult to evaluate because they sometimes display tortuosity even in normal populations. For these reasons, we recommend that the vertebral artery be evaluated.

An autosomal dominant genetic disorder, MFS has symptoms that include those of cardiovascular diseases (ascending aortic aneurysms, aortic dissections, mitral valve abnormalities), skeletal manifestations (pectus deformities, scoliosis, dolichostenomelia, arachnodactyly, joint laxity, highly arched palate), and ocular complications (ectopia lentis, retinal detachment, myopia). Diagnostic criteria for MFS, currently known as the Ghent criteria, emphasize the aortic aneurysms and dissections, a constellation of skeletal findings, ectopia lentis, dural ectasia, and the family history.[9] LDS has many similarities to MFS with regard to cardiovascular disorders or skeletal manifestations; therefore, if LDS patients did not show some characteristic manifestation, differentiation from MFS would be difficult without genetic analysis. Vertebral artery tortuosity may be the factor that can differentiate these disorders and so would be helpful in the clinical setting when genetic analysis is not immediately available.

Cardiovascular disease is more aggressive and widespread in LDS than MFS. Aortic rupture and dissection can occur in patients with aortic root diameters not considered at risk in MFS (<4.5 cm).[5] Recognition of LDS is important, especially for the management of these patients. The two major causes of death in LDS patients were reported to be aortic dissection and rupture in the thoracic (67%) and abdominal (22%) regions.[10] The third cause of mortality was intracranial hemorrhaging due to rupture of cranial arterial aneurysms (7%) because in LDS aneurysms are not confined to the aortic root, as with MFS, but occur throughout the entire arterial tree.

Our results indicated that peripheral aneurysms in LDS patients were present in the hepatic and mesenteric iliac arteries. These results were consistent with the fact that LDS has a high prevalence of peripheral aneurysms. The difference in the prevalence of peripheral aneurysms was not significant ($P = 0.057$), but it might be because the sample number was too small. It is important to know the prevalence of peripheral aneurysms for diagnosis and management.

Limitations

The number of patients in our sample was small, which was due to the requirement of genetic analysis to confirm the diagnosis of LDS and MFS in this study. Genetic analysis is not widely available in clinical settings. Also, bias may be present because our institution is a cardiovascular center. Hence, the patients referred to our hospital might have a higher prevalence of cardiovascular diseases than patients in other hospitals or institutions. Although the use of CT images for the initial diagnosis is preferred, because many of the LDS and MFS patients were referred to our hospital after the first operation we used the images obtained in the pre- or postoperative state. The mutation of TGFBR was classified as TGFBR-1 and TGFBR-2. Because both of these types have an aggressive vascular pathology, we did not mention the TGFBR types in this study. Further examination of a larger sample is needed to understand the relation between the gene type and the phenotype.

Conclusion

Vertebral artery tortuosity and peripheral aneurysms had a high prevalence among LDS patients. Identifying tortuosity in the vertebral artery has a potential to differentiate LDS from MFS. In the diagnosis of patients suspected of connective tissue disease, we should pay attention to peripheral artery diseases as well as aortic pathologies.

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Brief Report

Prenatal complex congenital heart disease with Loeys–Dietz syndrome

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Abstract We report an infantile case of Loeys–Dietz syndrome prenatally diagnosed with congenital complex heart disease – double outlet right ventricle and interruption of the aortic arch. The patient also showed prominent dilatation of the main pulmonary artery. Emergency bilateral pulmonary artery banding was performed on the 9th day. However, on the 21st day, the patient died of massive bleeding due to rupture of the right pulmonary artery. Subsequently, a mutation of the TGFBR1 gene was detected. As cardiovascular lesions of Loeys–Dietz syndrome appear early and progress rapidly, the prognosis is generally poor. Patients require periodic examination and early intervention with medical therapy such as Losartan administration and surgical therapy. Early genetic screening is thought to be useful for the prediction of complications as well as vascular disease.

Keywords: Prenatal diagnosis; aneurysm; chromosomal anomaly; connective tissue disorder

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Loeys–Dietz syndrome is a newly recognised, rare autosomal dominantly inherited connective tissue disorder caused by heterogeneous mutations in the genes encoding the transforming growth factor beta receptor one or two.[1] This syndrome is characterised by the triad of arterial tortuosity, aneurysm or dissections, hypertelorism, and bifid uvula or cleft palate.[2] Here, we present a patient prenatally diagnosed with complex congenital heart disease and confirmed with Loeys–Dietz syndrome after birth.

Case report

A 31-year-old pregnant woman was referred to our paediatric cardiology unit at the 36th week of gestation because of foetal congenital heart disease and dilatation of the pulmonary artery.

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The first foetal echocardiography revealed a huge aneurysm of the main pulmonary artery and complex congenital heart disease – double-outlet right ventricle and interruption of the aortic arch (Fig 1). Detailed multi-planar scanning showed that there was no pulmonary valve stenosis, because of no acceleration in pulmonic flow, and no absent pulmonary valve. Therefore, we suspected a connective tissue disorder, such as Marfan syndrome. The foetus was followed up weekly for foetal decompensation and signs of hydrops until the 39th week of gestation, and an elective caesarean section was then performed. The male infant weighed 2834 grams at birth. After delivery, the infant developed dyspnoea and was intubated for artificial ventilation. Subsequently, a cleft of the soft palate and bifid uvula were noted. To treat the interruption of the aortic arch, we started him on a prostaglandin infusion to maintain patent ductus arteriosus and on nitrogen inhalation to prevent pulmonary blood flow increase. Computed tomography and angiocardiography confirmed the heart

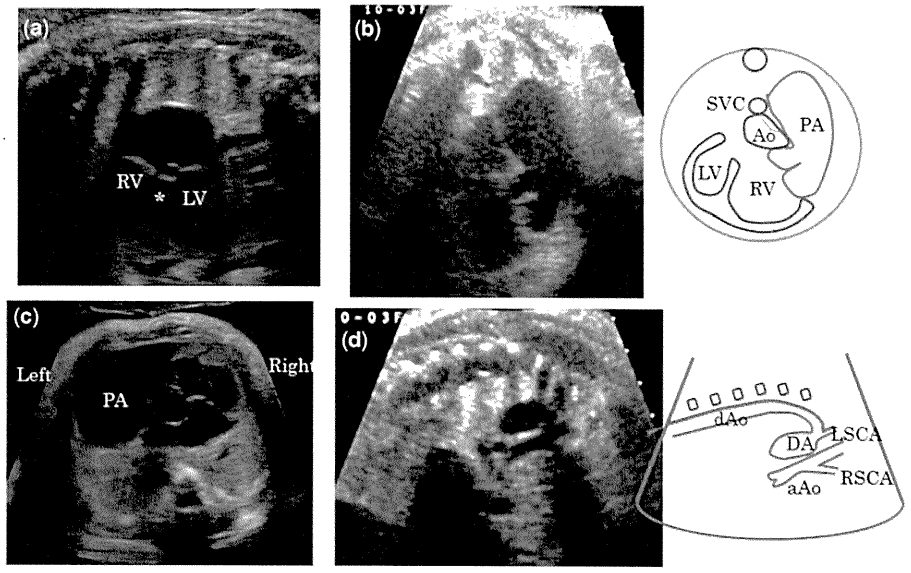

Figure 1.
Foetal echocardiography shows a large ventricular septal defect (*) of the double-outlet right ventricle (a), aneurysmal pulmonary artery (b, c), and interruption of the aortic arch (d). aAo = ascending aorta; Ao = aorta; DA = ductus arteriosus; dAo = descending aorta; LV = left ventricle; LSCA = left subclavian artery; PA = pulmonary artery; RSCA = right subclavian artery; RV = right ventricle; SVC = supra caval vein.

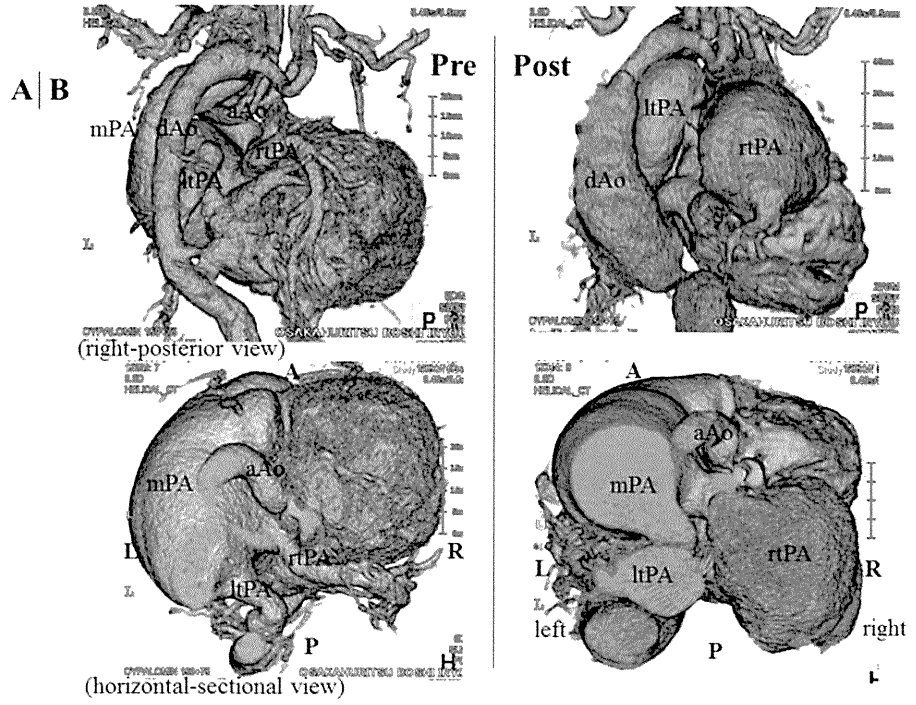

Figure 2.
Computed tomography (day 0) shows the interruption of the aortic arch and aneurysmal main pulmonary artery before operation (a). Computed tomography (day 18) shows progress of the significant expansion of the right and left pulmonary arteries and descending aorta after operation (b). A = anterior; aAo = ascending aorta; dAo = descending aorta; L = left; ltpa = left pulmonary artery; P = posterior; mPA = main pulmonary artery; rtPA = right pulmonary artery; R = right.

disease diagnosed prenatally (Fig 2a). Loeys–Dietz syndrome was strongly suspected because of the presence of cardiovascular lesions, thin skin, and facial appearance. On the 9th day, as the patient had suffered a pulmonary haemorrhage due to pulmonary blood flow increase, emergency bilateral