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Case Report

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Ruptured Vertebral Artery Aneurysm in a Patient with Loeys-Dietz Syndrome Type 4: A Sentinel Case Report

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ABSTRACT

Loey-Dietz Syndrome (LDS) is a rare, autosomal dominant connective tissue disorder with an estimated prevalence of less than 1 in 100,000. LDS results from one of several genetic mutations altering the transforming growth factor β (TGF- β) signaling pathway. LDS portends a higher risk of vascular pathology including dissections and aneurysms throughout the arterial system. Though not commonly described, this higher incidence of vascular pathology extends to the cerebrovascular system with several case reports of cerebral aneurysms in patients afflicted with LDS.

Herein, we describe the case of a 39-year-old female with a family history of cerebral and aortic aneurysms who presented with acute onset headache, neck pain, and lower extremity paresis prompting a CT head and subsequent magnetic resonance angiogram remarkable for a subarachnoid hemorrhage secondary to rupture of a large fusiform V4 segment vertebral artery aneurysm. Formal angiogram confirmed this diagnosis, and endovascular treatment was pursued with coil embolization of the aneurysm and parent vertebral artery distal occlusion. Subsequent genetic testing confirmed the patient to be positive for the mutation indicative of type 4 LDS.

Though rare, LDS should be considered as a possible diagnosis in patients presenting with aneurysmal subarachnoid hemorrhage when a family history of systemic vascular pathology is elicited. Confirmatory diagnosis of LDS appropriately spurs additional vascular imaging and family screening to proactively minimize the morbidity of this rare disease.

KEYWORDS: Loeys-Dietz Syndrome, Intracranial aneurysm, Endovascular neurosurgery

ABBREVIATIONS: LDS: Loeys-Dietz Syndrome, **TGF-β:** Transforming growth factor β, **ED:** Ehlers-Danlos Syndrome, **MEN2A:** Multiple endocrine neoplasia type 2A, **TGFβR1:** TGF-β receptor 1, **TGFβR2:** TGF-β receptor 2, **SMAD3:** Mothers against decapentaplegic homolog 3, **TGFβ2:** Transforming growth factor β2 ligand gene, **TGFβ3:**TGF-Beta 3 ligand gene, **FBN1:** Fibrillin 1 gene, **COL3A1:** Collagen Type III Alpha 1 Chain, **COL1A1:** Collagen Type I Alpha 1 Chain

INTRODUCTION

Looeys-Dietz Syndrome (LDS) is a rare autosomal dominant connective tissue disorder with a prevalence of less than 1 in 100,000 (11). LDS affects cardiovascular, craniofacial, cutaneous, ocular, and skeletal tissues. Individuals affected harbor a mutation in one of four genes involved in transforming growth factor β (TGF- β) signaling (11). Though typically associated with high risk of aortic dissections, affected individuals are also at risk of abnormal vasculature including aneurysms and dissections throughout the body's arterial network, including the cerebrovascular arterial tree. While similar to other connective tissue disorders associated with intracranial aneurysms such as Marfan Syndrome and

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Ehlers-Danlos Syndrome (EDS) type IV, a robust association has not yet been established between cerebrovascular arterial pathology and LDS. However, there are several case reports of intracranial aneurysms being treated in individuals with LDS (3,5,8). We describe the case of a 39-year-old female with previously undiagnosed LDS who presented with an intradural ruptured right vertebral artery aneurysm successfully treated with endovascular occlusion of the parent vessel.

CASE REPORT

A 39-year-old female with pertinent past medical history of multiple endocrine neoplasia type 2A (MEN2A) syndrome and medically controlled hypothyroidism status post thyroidectomy presented to the emergency department with severe headache, neck pain, photophobia, and paresis. Of note, the patient also had a significant family history of both aortic and cerebral aneurysms. On arrival to the emergency room, she had bilateral lower extremity weakness, but was otherwise neurologically intact. CT head revealed a subarachnoid hemorrhage ventral to the brainstem as well as some additional blood products posteriorly layering in the left lateral ventricle (Figure 1). Subsequent MR cervical spine demonstrated additional hemorrhage extending ventrally through the thecal sac to the thoracic spine. MRI/MRA head and neck revealed a 9 mm x 5mm aneurysm in the right V4 segment of the vertebral artery (Figure 2).

Following identification of the aneurysm, the patient underwent a formal digital subtraction angiogram which confirmed a fusiform, eccentric right vertebral artery dilatation measuring 8 x 7.5 x 9 mm just distal to the right posterior inferior cerebellar artery origin (Figure 3). A guide wire and microcatheter were successfully navigated into the right vertebral artery aneurysm. A series of coils were subsequently deployed into the aneurysm and parent vertebral artery with resultant sacrifice of the right vertebral artery distal to the aneurysm. Upon completion of coiling, complete flow obstruction to the right vertebral artery distal to the aneurysm was obtained (Figure 4A, B). A left vertebral artery injection revealed no retrograde flow into the aneurysm (Figure 4C, D).

Given the patient's significant family history of aortic and cerebral aneurysms as well as a subsequently elicited suspicion for a paternal history of connective tissue disease, Loeys-Dietz Syndrome was proposed as a possible underlying diagnosis and genetic counseling was obtained. While awaiting formal genetic testing results, a screening MR angiogram of the chest, abdomen, and pelvis was performed to assess the patient's systemic vasculature. The aortic arch, thoracic aorta, and abdominal aorta were all without evidence of aneurysm or dissection. However, the patient did have evidence of an 11cm splenic artery aneurysm and was appropriately scheduled with vascular surgery follow up. The patient was ultimately found to have a paternal lineage, pathogenic mutation in the TGFb2 gene. This gene mutation is passed down in the autosomal dominant fashion and diagnostic of Loeys-Dietz Syndrome type 4. (10)

DISCUSSION

LDS is a relatively new clinical entity with a highly aggressive vascular course. Originally described in 2005, LDS and its typical phenotypic manifestations are the result of variable expressivity mutations in multiple genes which alter TGF- β signaling resulting in altered cardiovascular, craniofacial, neurocognitive and skeletal development. (9) Individuals are predisposed to systemic arterial aneurysms and pregnancy-related complications including uterine rupture and death, as well as allergic/inflammatory diseases and increased incidence of gastrointestinal inflammation. Patients afflicted with LDS classically express the triad of hypertelorism, bifid uvu-

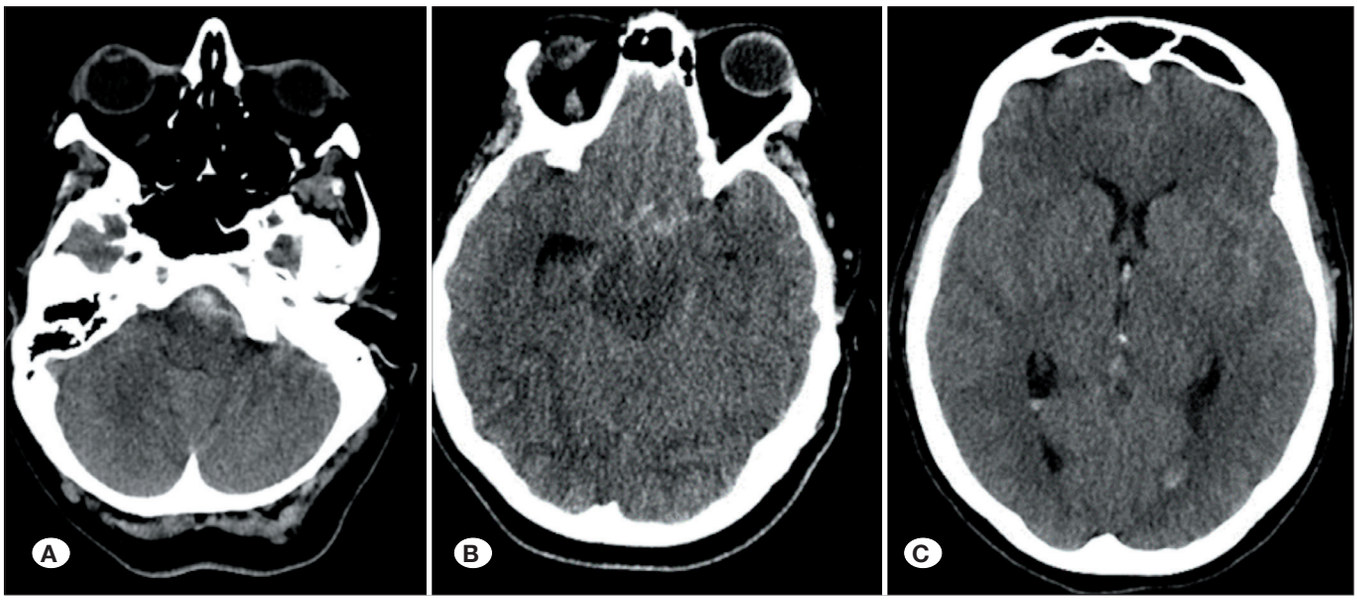

Figure 1: CT head without contrast. Series of axial views portraying subarachnoid hemorrhage ventral to the brainstem **(A,B)** along with layering of blood products within the posterior left lateral ventricle **(C)**.

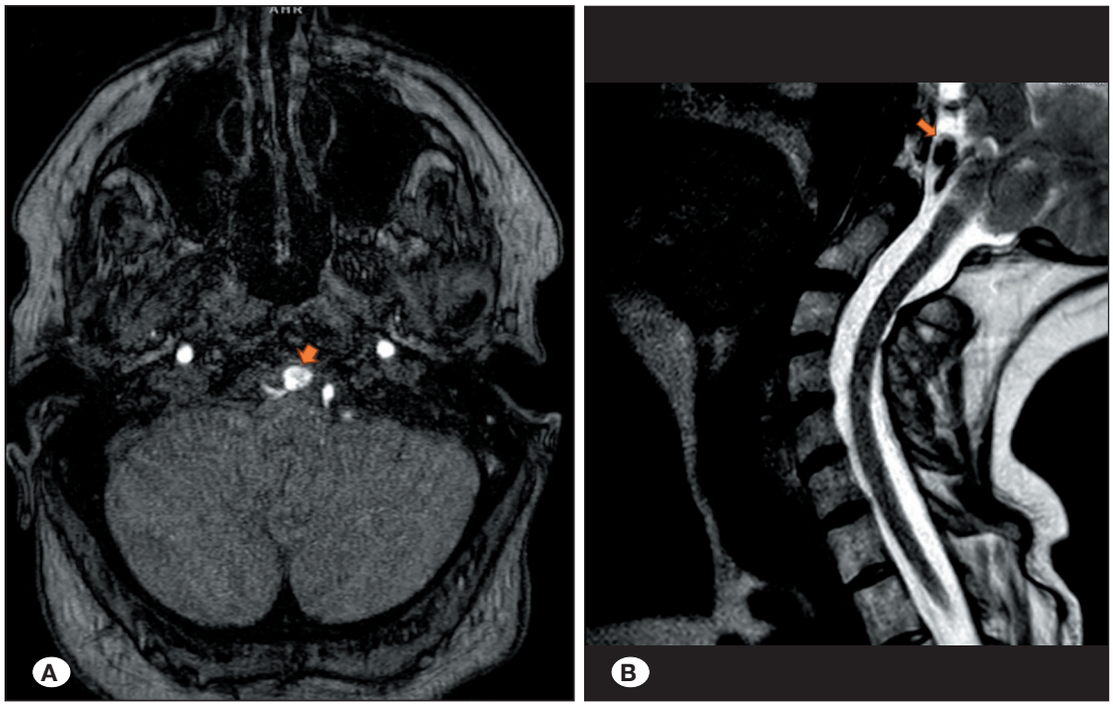

Figure 2: Magnetic Resonance Imaging (MRI) head and neck. **A)** MR Angiogram axial view reveals a 9 x 5 mm aneurysm in the right V4 segment of the vertebral artery (orange arrow). **B)** T2-Weighted MRI cervical spine sagittal view redemonstrating said aneurysm (orange arrow).

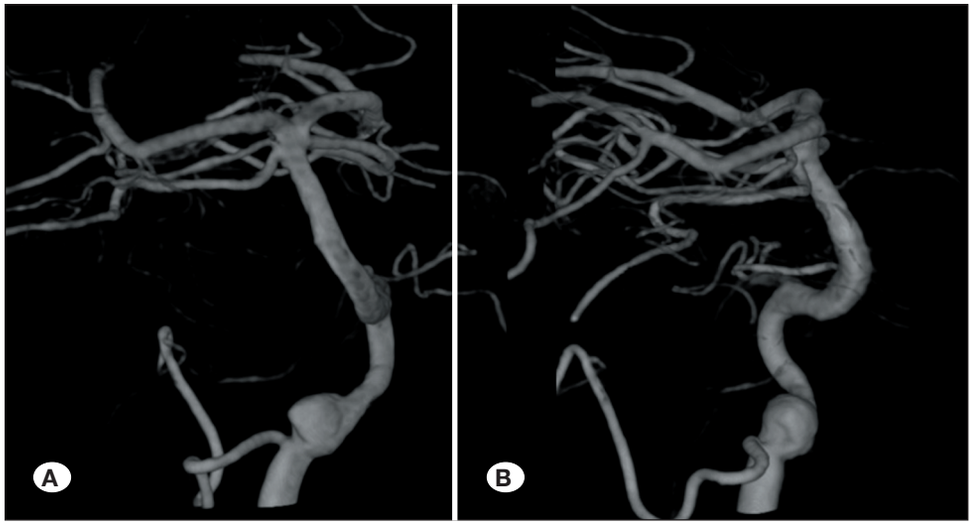

Figure 3: Digital Subtraction Angiogram with 3-dimensional reconstruction. **A)** Rotated antero-posterior and **B)** lateral views demonstrate a fusiform, eccentric right vertebral artery dilatation measuring 8 x 7.5 x 9 mm just distal to the right posterior inferior cerebellar artery origin.

la and or/cleft palate, and generalized arterial pathology. (13) At the time of its initial description, affected individuals were found to have heterozygous mutations in the genes encoding either the type I or type II TGF-b receptor, with the specific phenotypic manifestation being associated with the specific gene affected, resulting in two subtypes; LDS type 1 (mutation in TGF-b receptor 1 (TGFbR1)) and LDS type 2 (mutation in TGF-b receptor 2 (TGFbR2)). This classification system was subsequently expanded to include two additional subtypes, LDS type 3 and LDS type 4, which are associated with gene mutations in the mothers against decapentaplegic homolog 3 (SMAD3) gene and the transforming growth factor b2 ligand gene (TGFb2), respectively. (15) There has also been literature suggesting a fifth variant, LDS 5, which is associated with mutations in the TGF-Beta 3 ligand gene (TGFb3). (7) Regardless of the particular subtype, phenotypic manifestations are variable and range from mild to severe LDS independent of genotypic makeup. Patients most often present with thoracic aortic aneurysms and dissections, but as seen in our case, these are not always present. Surveillance for intracranial aneurysms

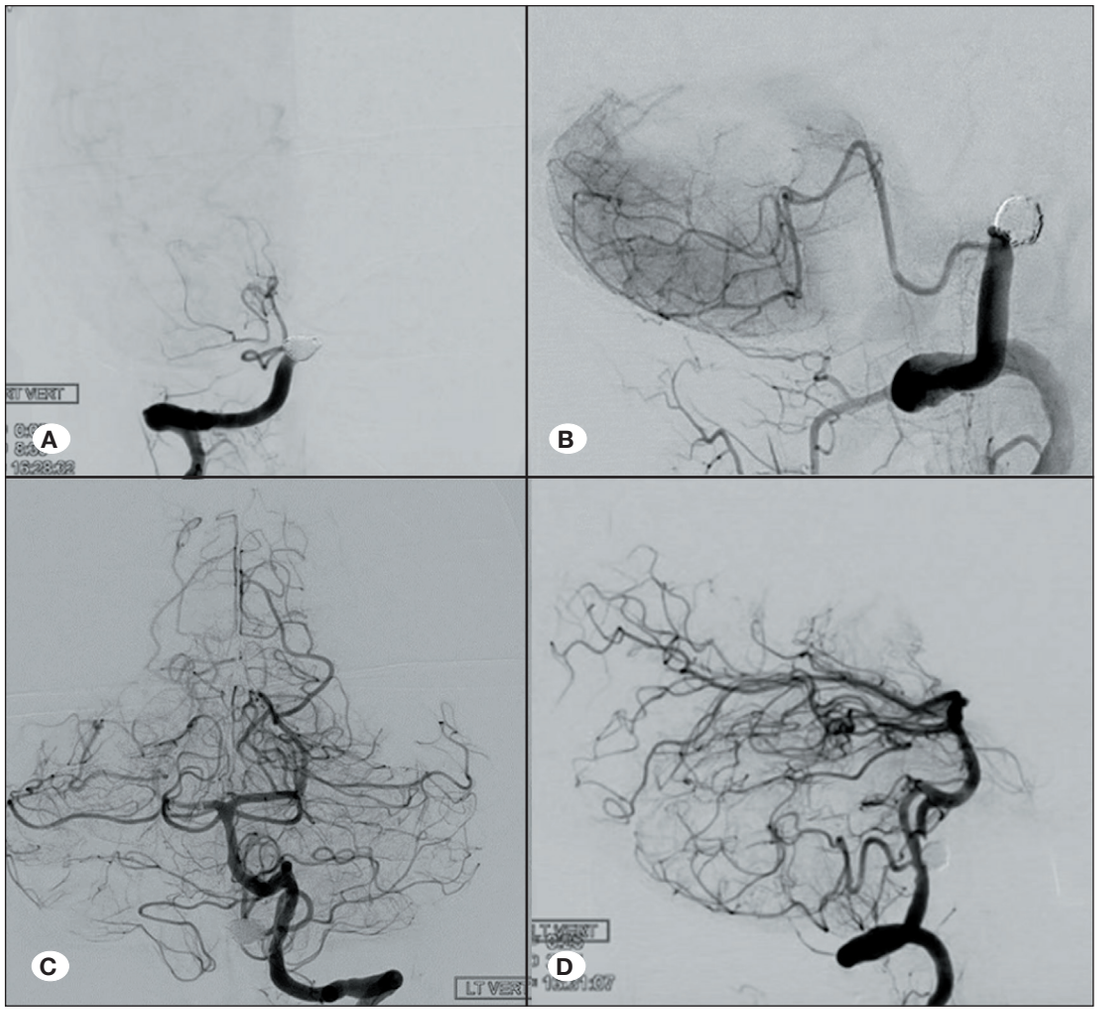

Figure 4: Post-embolization angiogram. **A)** Antero-posterior (AP) and **B)** lateral views of the right vertebral artery after coil embolization showing complete occlusion of the aneurysm along with the parent vessel distal to the aneurysm. **C)** AP and **D)** lateral left vertebral artery injections showing satisfactory perfusion of the posterior circulation via the left vertebral artery with no evidence of retrograde flow into the aneurysm.

should be implemented for all patients with LDS regardless of their genotypic type or phenotypic manifestations.

The first reported case of an intracranial aneurysm in an LDS patient was that of a 20-year-old female with a right carotid ophthalmic aneurysm and fusiform paraclinoid carotid aneurysm treated with an open aneurysm treatment approach. (14) In recent multicenter analyses, the prevalence rate of intracranial aneurysms in LDS patients has been found to be 23-30%. (13) Other studies have shown a significant presence of Chiari malformation type I with those LDS patients who were found to have intracranial aneurysms. (6)

Treatment of intracranial aneurysms in patients with LDS has been accomplished through both open and endovascular methods. Cases have reported successful treatment of aneurysms in LDS patients via open craniotomy and clipping. (5) There have also been reports of successful aneurysm embolization via stent assisted coiling in this patient population. (8) Furthermore, there have been reports of utilizing the pipeline embolization device for flow diversion and curative parent vessel reconstruction in LDS patients without evidence of injury or vessel dissection. (3) This report details the novel case of an adult patient with LDS4 successfully treated for a ruptured vertebral artery aneurysm. Intracranial aneurysm treatment in a patient with LDS 4 has not yet been described.

LDS has a close connection with other connective tissue disorders, having at one point thought to have been a variant of Marfan Syndrome and often being misdiagnosed as such. Each child of an individual with LDS has a 50% chance of developing the pathogenic variant of the disorder. Marfan Syndrome is also inherited in an autosomal dominant fashion and involves skeletal, cardiovascular, and ocular systems, but is caused by a mutation in the fibrillin 1 gene (FBN1) coding for extracellular matrix protein fibrillin-1. (4) Interestingly, the mutation in fibrillin-1 leads to enhanced TGFb signaling, prominently contributing to the pathology of Marfan Syndrome, whereas cytoplasmic kinase mutations in the TGF-b receptors

or ligands are the underlying cause of LDS. (2) Marfan Syndrome is not associated with brain aneurysms, further supporting the role of TGF-b in brain aneurysm formation and the role mutations in signaling pathways can have on clinical presentation.

CONCLUSION

Vascular Ehlers-Danlos Syndrome can also clinically resemble LDS, but is characterized by pathogenic variance in the COL3A1 or COL1A1 genes, which play a role in collagen formation. (1) The TGF-b pathway is an important mediator of immunological maturity, cancer, inflammation and fibrosis, in addition to skeletal, vascular and hematopoietic homeostasis. (12) Further exploration of this pathway and its regulators could lead to novel therapeutic options for connective tissue disorders such as LDS and better understanding of the mechanisms underlying aneurysm formation.

Declarations

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Informed consent: Written informed consents were obtained from the individuals (and/or legal representatives) for the publication of the cases.

AUTHORSHIP CONTRIBUTION

Study conception and design: EEW, LS, JM, BL
Data collection: EEW, LS, ED, JM
Analysis and interpretation of results: EEW, LS, BL, BT
Draft manuscript preparation: EEW, LS
Critical revision of the article: EEW, LS, ED, JM, BL, BT
Other (study supervision, fundings, materials, etc...): BL, BT
All authors (EEW, LS, ED, JM, BL, BT) reviewed the results and approved the final version of the manuscript.

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