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Review

Clinical features and complications of Loeys-Dietz syndrome: A systematic review

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ABSTRACT

Introduction: Loeys-Dietz syndrome (LDS) is a connective tissue disorder that arises from mutations altering the transforming growth factor β signalling pathway. Due to the recent discovery of the underlying genetic mutations leading to LDS, the spectrum of characteristics and complications is not fully understood.
Methods: Our search included five databases (Pubmed, SCOPUS, Web of Science, EMBASE and google scholar) and included variations of "Loeys-Dietz Syndrome" as search terms, using all available data until February 2021. All study types were included. Three reviewers screened 1394 abstracts, of which 418 underwent full-text review and 392 were included in the final analysis.
Results: We identified 3896 reported cases of LDS with the most commonly reported features and complications being: aortic aneurysms and dissections, arterial tortuosity, high arched palate, abnormal uvula and hypertelorism. LDS Types 1 and 2 share many clinical features, LDS Type 2 appears to have a more aggressive aortic disease. LDS Type 3 demonstrated an increased prevalence of mitral valve prolapse and arthritis. LDS Type 4 and 5 demonstrated a lower prevalence of musculoskeletal and cardiovascular involvement. Amongst 222 women who underwent 522 pregnancies, 4% experienced an aortic dissection and the peripartum mortality rate was 1%.
Conclusion: We observed that LDS is a multisystem connective tissue disorder that is associated with a high burden of complications, requiring a multidisciplinary approach. Ongoing attempts to better characterise these features will allow clinicians to appropriately screen and manage these complications.

1. Introduction

Loeys-Dietz syndrome (LDS) is an autosomal dominant connective disorder that has been associated with extensive systemic involvement including craniofacial, skeletal, cutaneous and vascular (arterial tortuosity, aneurysm formation and dissection) abnormalities. Since this disease entity has been identified (1,2), multiple additional gene mutations have been identified with unique characteristics, further differentiating LDS into types one to five (3–5). The subtypes of LDS illustrate the spectrum of the disorder, with type 1 being the most severe phenotype and type 5 being the least. LDS type 1 has been associated with mutations in the transforming growth factor β (TGFB) receptor one (TGFBR1) and is characterised by the presence of craniofacial abnormalities whereas LDS type 2 is associated with mutations in transforming growth factor β receptor two (TGFBR2) which is associated with minimal craniofacial abnormalities. Of note, early categorisation of LDS was based on the absence or presence of craniofacial features regardless of genetic mutations (1). However, LDS type 3 was found to be associated with mothers against decapentaplegic homolog (SMAD) 3 mutations, with prominent features of osteoarthritis. LDS type 4 and 5 are associated with mutations in TGFB 2 and 3 ligand respectively. Of note, SMAD2 mutations have been identified to be associated with clinical features of LDS, but have yet to be placed on the spectrum of LDS subtypes (6). Due to a paucity of large observational studies, the full clinical spectrum of LDS is unknown.

While rare, the prevalence of LDS is unknown and there is a paucity of data to characterise these individuals and their complications, limited to small cohorts and case reports. Our objective was to systematically describe the clinical features and complications of patients with genetically confirmed LDS, which may supplement current recommendations for diagnosis and management of this condition (7,8).

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2. Methods

2.1. Systematic review

The search strategy was conducted in accordance to the PRISMA-S extension of the PRISMA statement for reporting literature searches in systematic reviews (9). This review was prospectively registered with PROSPERO, an international prospective register of systematic reviews (CRD42021247713).

2.2. Data sources and searches

The following databases were searched: Pubmed, SCOPUS, Web of Science, EMBASE and google scholar. No study registries or other online resources were searched. Cited references in identified articles were visually screened for additional references. No additional studies were sought by contacting authors. The individual search strategy for each database can be seen in Supplementary Table 1. In brief, using the search terms "loeys-dietz syndrome", "loeys-dietz", "loeys dietz syndrome" and "loeys dietz" were utilised with no date, language, study design filters. All original searches were conducted on February 6, 2021. Email alerts from each database were utilised to update the search during the study period. A specialised librarian at the University of Alberta reviewed the search strategy.

All studies were included if they described clinical features or complications of a subject with genetically confirmed LDS. All study types were included. Conference abstracts were excluded if a subsequent full manuscript was identified. Cases of reported genetically-confirmed cases of LDS, without further elaboration on genetic mutation or LDS classification were included to identify the largest possible cohort of patients with LDS, but are labelled as LDS "unknown".

The final search identified 4049 references, of which 2655 were duplicate references (Supplementary Fig. 1). The remaining 1394 references were loading into the Covidence systematic review manager for title and abstract screening. Each record was reviewed by two investigators for inclusion and exclusion criteria. In the event of discordance, a third investigator was assigned followed by a discussion to reach a consensus. In total, 418 manuscripts were identified for full-text review, which included an additional 17 manuscripts from e-mail alerts/reference lists. During full-text review, a further 26 were excluded due to duplicates ($n = 14$) and inability to extract any data regarding individuals with LDS due to amalgamated data ($n = 12$). The resultant 392 manuscripts were included for further analysis.

2.3. Data extraction and quality assessment

Three reviewers independently extracted data from each included manuscript using an internally validated case report form. The case report form was formed based on a comprehensive review of the literature identifying characteristics and complications of interest (Table 1). The case report form was subsequently trialled by four data abstractors on ten of the included articles in this review. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of Alberta (10). REDCap is a secure, web-based software platform designed to support data capture for research studies. In brief, data on clinical characteristics, genetic testing and complications were extracted. In the event of a manuscript that presents amalgamated data, details of the population cohort were also extracted. Where possible data regarding prevalence in comparison to other connective tissue disorders was also extracted.

Methodological quality of reporting was assessed using components of the Case Report (CARE) guidelines and with reviewers asked to subjectively assess each manuscript to have either a low, intermediate or high risk of reporting bias (11). High-quality studies were defined as those demonstrating a low-risk of reporting bias.

2.4. Data synthesis and analysis

Counts of clinical features and complications were identified in the overall population, stratified by LDS type and by study type (individual data available versus amalgamated data from cohort studies).

2.5. Funding

No funding was received for this work.

3. Results

Of the 392 manuscripts, 266 (68%) were case reports/series with individual-level data and 126 (32%) were reports of cohort studies with amalgamated data on patients with LDS. The majority of included studies demonstrated a high risk of bias ($n = 196$; 50%), with the remaining demonstrating intermediate ($n = 110$; 28%) or low ($n = 86$; 22%) risk of bias. Cohort studies were more frequently reported as having a high-risk of bias ($n = 95$; 75%) compared to individual-level studies ($n = 101$; 38%).

In the 266 individual level data manuscripts, 391 individuals with LDS were identified of which 69 (18%) had LDS type 1, 164 (42%) LDS type 2, 39 (10%) LDS type 3, 24 (6%) LDS type 4, 6 (2%) LDS type 5 and 89 (23%) were unknown. In the 126 cohort manuscripts, 3505 individuals with LDS were identified, of which 614 (18%) had LDS type 1, 1057 (30%) LDS type 2, 264 (8%) LDS type 3, 130 (4%) LDS type 4, 79 (2%) LDS type 5 and 1361 (39%) were unknown. The overall prevalence of characteristics and complications of LDS can be seen in Table 1. Due to the high risk of bias due to incomplete reporting, we provide a narrative review of characteristics and complications by LDS type and system involvement. The frequency of observed features and complications stratified by LDS type in individual studies (Table 2) and high-quality cohort studies (Table 3, Supplementary Tables 3–7).

3.1. LDS characteristics by genetic mutation

3.1.1. LDS type 1

LDS Type 1 is the results of a mutation in TGFBR1. Amongst individual case reports, the most frequently reported physical characteristics include: aortic aneurysms, abnormal uvula, arterial tortuosity, pectus deformity and arachnodactyly (Table 2). In cohort studies of patients with LDS type 1 (1,2,12–15), ranging from 12 to 176 individuals (Supplementary Table 3), the most frequently reported characteristics include: joint laxity (68%), arachnodactyly (62%), pectus deformity (51%), aneurysms of vessels other than the aorta (50%), arterial tortuosity (50%) and retrognathia (50%; Table 3). The presence of aortic aneurysms varied significantly between studies ranging from 17 to 100% and aortic dissections ranged from 17 to 25%.

3.1.2. LDS type 2

LDS Type 2 is the results of a mutation in TGFBR2. The most frequently reported physical characteristics include: aortic aneurysms, hypertelorism, abnormal uvula, joint laxity, pectus deformity, scoliosis, arterial tortuosity, arachnodactyly (Table 2). In cohort studies of patients with LDS type 2 (1,2,12,14–16), ranging from 12 to 265 patients (Supplementary Table 4), the most frequently reported features include: velvety skin (82%), malar hypoplasia (75%), easy bruising (67%), aneurysms of vessels other than the aorta (59%), arterial tortuosity (49%), high arched palate (48%) and pectus deformity (47%; Table 3). The prevalence of aortic aneurysm ranged from 23 to 75% as did a history of aortic dissection 16–35%.

3.1.3. LDS type 3

LDS Type 3 (previously known as aneurysms-osteoarthritis syndrome) is the result of mutations in the SMAD3 gene. There were few reported individual cases of LDS Type 3 ($n = 39$), with only a quarter

Table 1
Clinical features and complications of patients with LDS.

	Individual Cases (n = 391)				Cohort Cases (n = 3505)	Total (n = 3896)
	Present	Absent	Frequency	Valid Frequency[a]		
Aortic aneurysm	275	10	70.3%	96.5%	1058 (30%)	1333 (34%)
Pulmonary artery aneurysm	25	28	6.4%	47.2%	9 (0%)	34 (1%)
Descending aortic aneurysm	41	21	10.5%	66.1%	50 (1%)	91 (2%)
Subclavian artery aneurysm	20	25	5.1%	44.4%	13 (0%)	33 (1%)
Superior mesenteric artery aneurysm	7	24	1.8%	22.6%	5 (0%)	12 (0%)
Cerebral aneurysm	25	23	6.4%	52.1%	48 (1%)	73 (2%)
Other vessel aneurysm	59	23	15.1%	72.0%	96 (3%)	155 (4%)
Aortic dissection	80	26	20.5%	75.5%	337 (10%)	417 (11%)
Other vessel dissection	28	22	7.2%	56.0%	52 (1%)	80 (2%)
Arterial tortuosity	93	32	23.8%	74.4%	347 (10%)	440 (11%)
Mitral valve prolapse	28	37	7.2%	43.1%	254 (7%)	282 (7%)
Bicuspid aortic valve	12	34	3.1%	26.1%	22 (1%)	34 (1%)
Aortic insufficiency	48	17	12.3%	73.8%	27 (1%)	75 (2%)
Bicuspid pulmonary valve	0	27	0%	0%	1 (0%)	1 (0%)
Pulmonary valve stenosis	0	25	0%	0%	2 (0%)	2 (0%)
Persistent ductus arteriosus	38	32	9.7%	54.3%	40 (1%)	78 (2%)
Left ventricular hypertrophy	2	24	0.5%	7.7%	11 (0%)	13 (0%)
Atrial fibrillation	2	23	0.5%	8.0%	13 (0%)	15 (0%)
Atrial septal defect	25	47	6.4%	34.7%	71 (2%)	96 (2%)
Cardiac arrest/VT/VF	3	24	0.8%	11.1%	1 (0%)	4 (0%)
Dolichostenomelia	19	48	4.9%	28.4%	30 (1%)	49 (1%)
Arachnodactyly	78	43	19.9%	64.5%	97 (3%)	175 (4%)
Pectus deformity	108	33	27.6%	76.6%	190 (5%)	298 (8%)
Scoliosis	95	3	24.3%	96.9%	214 (6%)	309 (8%)
Camptodactyly	44	41	11.3%	51.8%	24 (1%)	68 (2%)
Joint laxity (Beighton score 5+/9)	120	38	30.7%	75.9%	63 (2%)	183 (5%)
Protrusio acetabulae	3	32	0.8%	8.6%	22 (1%)	25 (1%)
Pes planus	27	31	6.9%	46.6%	115 (3%)	142 (4%)
Osteoporosis	3	25	0.8%	10.7%	0 (0%)	3 (0%)
Osteoarthritis	8	27	2.0%	22.9%	69 (2%)	77 (2%)
Intervertebral disc degeneration	2	23	0.5%	8.0%	18 (1%)	20 (2%)
Spondyloses	1	24	0.3%	4.0%	39 (1%)	40 (1%)
Spondylolisthesis	4	24	1.0%	14.3%	31 (1%)	35 (1%)
Meniscal lesions	0	24	0%	0%	6 (0%)	6 (0%)
Osteochondritis dissecans	0	24	0%	0%	11 (0%)	11 (0%)
Talipes equinovarus	57	52	14.6%	52.3%	39 1%)	96 (2%)
Cervical-spine instability	20	42	5.1%	32.3%	57 (2%)	77 (2%)
Postaxial polydactyly	0	26	0%	0%	1 (0%)	1 (0%)
Hypertelorism	112	46	28.6%	70.9%	265 (7%)	377 (10%)
Abnormal uvula	127	42	32.5%	75.1%	276 (8%)	403 (10%)
Cleft palate	47	47	12.0%	50.0%	58 (2%)	105 (3%)
High arched palate	56	41	14.3%	57.7%	340 (10%)	396 (10%)
Dental malocclusion	9	27	2.3%	25.0%	62 (2%)	71 (2%)
Malar hypoplasia	36	48	9.2%	42.9%	123 (3%)	159 (4%)
Retrognathia	58	42	14.8%	58.0%	91 (3%)	149 (4%)
Blue sclerae	35	48	9.0%	42.2%	57 (2%)	92 (2%)
Ectopia lentis	3	61	0.8%	4.7%	1 (0%)	4 (0%)
Craniosynostosis	44	47	11.3%	48.4%	92 (3%)	136 (3%)
Exotropia	28	28	7.2%	50.0%	31 (1%)	59 (2%)
Velvety skin	19	48	4.9%	28.4%	57 (2%)	76 (2%)
Easy bruising	16	25	4.1%	39.0%	29 (1%)	45 (1%)
Atrophic scars	9	24	2.3%	27.3%	102 (3%)	111 (3%)
Striae	19	27	4.9%	41.3%	74 (2%)	93 (2%)
Umbilical/inguinal hernia	56	23	14.3%	70.9%	99 (3%)	155 (4%)
Translucent skin	35	40	9.2%	46.7%	151 (4%)	186 (5%)
Dural ectasia	15	36	3.8%	29.4%	95 (3%)	110 (3%)
Developmental delay	14	47	3.6%	23.0%	73 (2%)	87 (2%)
Chiari malformation	5	28	1.3%	15.2%	4 (0%)	9 (0%)
Hydrocephalus	2	31	0.5%	6.1%	7 (0%)	9 (0%)
Bladder prolapse	0	24	0%	0%	0 (0%)	0 (0%)
Uterine prolapse	1	24	0.3%	4.0%	0 (0%)	1 (0%)
Bowel prolapse	0	24	0%	0%	0 (0%)	0 (0%)
Varices	0	24	0%	0%	15 (0%)	15 (0%)
Food allergies	2	23	0.5%	8.0%	1 (0%)	3 (0%)
Seasonal allergies	1	23	0.3%	4.2%	44 (1%)	45 (1%)
Asthma / chronic sinusitis	13	22	3.3%	37.1%	30 (1%)	43 (1%)
Eczema	4	23	1.0%	14.8%	22 (1%)	26 (1%)
Eosinophilic esophagitis/gastritis	4	24	1.0%	14.3%	6 (0%)	10 (0%)
Inflammatory bowel disease	8	24	2.0%	25.0%	0 (0%)	8 (0%)

Abbreviations: VT – ventricular tachycardia; VF – Ventricular fibrillation.

[a] Valid frequency is defined is [absent / (absent + present)], excluding cases where the absence of presence of a feature is undocumented.

Table 2
Frequency of characteristics and complications by LDS type in individual level studies.

	LDS Type 1		LDS Type 2		LDS Type 3		LDS Type 4		LDS Type 5	
	All ($n = 69$)	High quality ($n = 21$)	All ($n = 164$)	High quality ($n = 64$)	All (n = 39)	High quality (n = 10)	All ($n = 24$)	High quality ($n = 18$)	All (n = 6)	High quality (n = 3)
Aortic aneurysm	44 (64%)	18 (86%)	130 (79%)	54 (84%)	21 (54%)	4 (40%)	17 (71%)	11 (61%)	3 (50%)	1 (33%)
Pulmonary artery aneurysm	3 (4%)	1 (5%)	15 (9%)	9 (14%)	0 (0%)	0 (0%)	3 (13%)	1 (6%)	0 (0%)	0 (0%)
Subclavian artery aneurysm	0 (0%)	0 (0%)	9 (5%)	2 (3%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cerebral aneurysm	4 (6%)	0 (0%)	9 (5%)	3 (5%)	3 (8%)	1 (10%)	3 (13%)	3 (17%)	0 (0%)	0 (0%)
Other vessel aneurysm	8 (12%)	2 (10%)	20 (12%)	6 (9%)	8 (21%)	4 (40%)	5 (21%)	5 (28%)	0 (0%)	0 (0%)
Aortic dissection	15 (22%)	5 (24%)	31 (19%)	9 (14%)	13 (33%)	3 (30%)	1 (4%)	1 (6%)	1 (17%)	0 (0%)
Other vessel dissection	5 (7%)	2 (10%)	8 (5%)	4 (6%)	7 (18%)	1 (10%)	1 (4%)	1 (6%)	1 (17%)	0 (0%)
Arterial tortuosity	19 (28%)	9 (43%)	49 (30%)	24 (38%)	4 (10%)	2 (20%)	10 (42%)	739%)	0 (0%)	0 (0%)
Mitral valve prolapse	5 (7%)	1 (5%)	8 (5%)	4 (6%)	5 (13%)	1 (10%)	5 (21%)	4 (22%)	1 (17%)	1 (33%)
Bicuspid aortic valve	2 (3%)	0 (0%)	5 (3%)	1 (2%)	1 (3%)	0 (0%)	2 (8%)	2 (11%)	0 (0%)	0 (0%)
Aortic insufficiency	12 (17%)	3 (14%)	16 (10%)	5 (8%)	4 (10%)	0 (0%)	1 (4%)	0 (0%)	1 (17%)	1 (33%)
Bicuspid pulmonary valve	6 (9%)	2 (10%)	7 (4%)	5 (8%)	2 (5%)	1 (10%)	1 (4%)	1 (6%)	0 (0%)	0 (0%)
Persistent ductus arteriosus	4 (6%)	2 (10%)	29 (18%)	14 (22%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Atrial septal defect	4 (6%)	1 (5%)	14 (9%)	3 (5%)	3 (8%)	1 (10%)	1 (4%)	0 (0%)	1 (17%)	1 (33%)
Dolichostenomelia	3 (4%)	2 (10%)	11 (7%)	7 (11%)	3 (8%)	1 (10%)	1 (4%)	1 (6%)	0 (0%)	0 (0%)
Arachnodactyly	17 (25%)	8 (38%)	43 (26%)	24 (38%)	3 (8%)	2 (20%)	6 (25%)	4 (22%)	3 (50%)	2 (67%)
Pectus deformity	22 (32%)	13 (62%)	54 (33%)	26 (41%)	6 (15%)	3 (30%)	8 (33%)	8 (44%)	5 (83%)	3 (100%)
Scoliosis	13 (19%)	8 (38%)	51 (31%)	31 (48%)	4 (10%)	2 (20%)	9 (38%)	9 (50%)	4 (67%)	2 (67%)
Camptodactyly	2 (3%)	1 (5%)	37 (23%)	22 (34%)	0 (0%)	0 (0%)	1 (4%)	1 (6%)	1 (17%)	1 (33%)
Joint laxity (Beighton score 5+/9)	22 (32%)	10 (48%)	64 (39%)	34 (53%)	3 (8%)	2 (20%)	15 (63%)	12 (67%)	4 (67%)	3 (100%)
Pes planus	3 (4%)	2 (10%)	6 (4%)	3 (5%)	7 (18%)	1 (10%)	6 (25%)	6 (33%)	2 (33%)	2 (67%)
Meniscal lesions	4 (6%)	0 (0%)	6 (4%)	3 (5%)	2 (5%)	1 (10%)	1 (4%)	1 (6%)	0 (0%)	0 (0%)
Talipes equinovarus	9 (13%)	3 (14%)	42 (26%)	20 (31%)	1 (3%)	1 (10%)	2 (8%)	2 (11%)	0 (0%)	0 (0%)
Cervical-spine instability	2 (3%)	1 (5%)	16 (10%)	11 (17%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Postaxial polydactyly	5 (7%)	1 (5%)	7 (4%)	4 (6%)	2 (5%)	1 (10%)	1 (4%)	1 (6%)	0 (0%)	0 (0%)
Hypertelorism	19 (28%)	6 (29%)	70 (43%)	35 (55%)	3 (8%)	1 (10%)	5 (21%)	3 (17%)	3 (50%)	2 (67%)
Abnormal uvula	31 (45%)	11 (52%)	71 (43%)	40 (63%)	5 (13%)	1 (10%)	1 (4%)	1 (6%)	6 (100%)	3 (100%)
Cleft palate	7 (10%)	4 (19%)	33 (20%)	19 (30%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (50%)	2 (67%)
High arched palate	13 (19%)	4 (19%)	28 (17%)	15 (23%)	3 (8%)	1 (10%)	6 (25%)	5 (28%)	0 (0%)	0 (0%)
Malar hypoplasia	15 (22%)	8 (38%)	16 (10%)	12 (19%)	0 (0%)	0 (0%)	4 (17%)	3 (17%)	0 (0%)	0 (0%)
Retrognathia	14 (20%)	7 (33%)	36 (22%)	19 (30%)	0 (0%)	0 (0%)	6 (25%)	5 (28%)	1 (17%)	1 (33%)
Blue sclerae	8 (12%)	5 (24%)	23 (14%)	17 (27%)	0 (0%)	0 (0%)	3 (13%)	3 (17%)	1 (17%)	1 (33%)
Craniosynostosis	16 (23%)	7 (33%)	23 (14%)	12 (19%)	0 (0%)	0 (0%)	2 (8%)	1 (6%)	0 (0%)	0 (0%)
Exotropia	5 (7%)	2 (10%)	19 (12%)	9 (14%)	0 (0%)	0 (0%)	3 (13%)	3 (17%)	0 (0%)	0 (0%)
Velvety skin	5 (7%)	1 (5%)	12 (7%)	6 (9%)	1 (3%)	1 (10%)	1 (4%)	1 (6%)	0 (0%)	0 (0%)
Easy bruising	0 (0%)	0 (0%)	9 (5%)	5 (8%)	1 (3%)	0 (0%)	5 (21%)	5 (28%)	0 (0%)	0 (0%)
Striae	2 (3%)	2 (10%)	6 (4%)	5 (8%)	7 (18%)	1 (10%)	4 (17%)	4 (22%)	0 (0%)	0 (0%)
Umbilical/inguinal hernia	11 (16%)	6 (29%)	30 (18%)	14 (22%)	4 (10%)	1 (10%)	7 (29%)	7 (39%)	2 (33%)	1 (33%)
Translucent skin	8 (12%)	5 (24%)	17 (10%)	8 (13%)	2 (5%)	1 (10%)	4 (17%)	2 (11%)	1 (17%)	1 (33%)
Dural ectasia	3 (4%)	1 (5%)	7 (4%)	4 (6%)	1 (3%)	0 (0%)	3 (13%)	2 (11%)	0 (0%)	0 (0%)
Developmental delay	7 (10%)	4 (19%)	5 (3%)	2 (3%)	1 (3%)	1 (10%)	1 (4%)	1 (6%)	0 (0%)	0 (0%)
Asthma / chronic sinusitis	4 (6%)	3 (14%)	3 (2%)	1 (2%)	1 (3%)	1 (10%)	3 (13%)	3 (17%)	0 (0%)	0 (0%)

Variables with a frequency of <10 across all LDS types removed including: superior mesenteric artery aneurysm, left ventricular hypertrophy, atrial fibrillation, cardiac arrest, protrusio acetabulae, osteoporosis, osteoarthritis, intervertebral disc degeneration, spondyloses, spondylolisthesis, dental malocclusion, ectopia lentis, atrophic scars, Chiari malformation, hydrocephalus, uterine/bladder/bowel prolapse, varices, food allergies, eczema, eosinophilic esophagitis/gastritis, inflammatory bowel disease.

considered high quality, leading to low quality prevalence estimates from the summation of these studies (Table 2). Amongst high-quality cohort studies (14,15,17–19), that ranged from 9 to 45 individuals (Supplementary Table 5), we observe that this cohort is uniquely characterised by the presence of early onset osteoarthritis (41–96%) and osteochondritis dissecans (56%), which is frequently the symptoms that leads them to present for medical consultation (Table 3). In addition, they demonstrated a high frequency of aortic aneurysms (50–79%), and arterial tortuosity of the cerebral arteries (50%). Aortic dissections were reported to occur in 0–33% of individuals. Patients with LDS type 3 demonstrate the highest prevalence of mitral valve prolapse (41% in cohort studies), compared to other types of LDS. Other common phenotypic anomalies included: varices (58%), striae (20–53%), velvety skin (58–62%), abnormal uvula (11–52%), abnormal palate (53–60%),

Table 3
Amalgamated data from cohort studies of high quality.

	LDS Type 1 (*n* = 306)	LDS Type 2 (*n* = 414)	LDS Type 3 (*n* = 133)	LDS Type 4 (*n* = 67)	LDS Type 5 (*n* = 75)
Aortic aneurysm	105/282 (37%)	153/398 (38%)	54/87 (62%)	32/60 (53%)	17/75 (23%)
Other vessel aneurysm	26/52 (50%)	13/22 (59%)	4/20 (20%)	4/57 (7%)	4/75 (5%)
Aortic dissection	47/252 (19%)	53/303 (7%)	16/87 (18%)	4/42 (10%)	10/43 (23%)
Arterial tortuosity	91/183 (50%	88/178 (49%)	11/36 (31%)	6//42 (14%)	2/32 (6%)
Mitral valve prolapse	48/222 (22%)	98/360 (27%)	41/101 (41%)	11//34 (32%)	11/75 (15)
Bicuspid aortic valve	1/26 (4%)	7/111 (6%)	2/17 (12%)	3/18 (17%)	
Arachnodactyly	33/52 (63%)	34/82 (41%)	21/61 (34%)	8/15 (53%)	35/75 (47%)
Pectus deformity	41/80 (51%)	38/81 (47%)	30/79 (38%)	13/ 34 (38%)	25/75 (33%)
Scoliosis	34/80 (42%)	29/80 (36%)	41/84 (49%)	10/37 (27%)	20/75 (27%)
Camptodactyly	15/40 (38%)		4/30 (13%)		3/75 (4%)
Joint laxity (Beighton score 5+/9)	27/40 (68%)	12/12 (100%)	12/51 (24%)	20/37 (54%)	25/75 (33%)
Pes planus	11/28 (41%)		34/50 (68%)	20/37 (54%)	23/75 (31%)
Osteoporosis/ osteopenia			5/9 (56%)		
Osteoarthritis	0/11 (0%)	0/10 (0%)	35/49 (71%)		5/75 (7%)
Talipes equinovarus	19/52 (37%)	5/12 (42%)	2/19 (11%)	5/15 (33%)	4/75 (5%)
Cervical-spine instability	8/51 (16%)	2/9 (22%)	0/9 (0%)		2/43 (5%)
Hypertelorism	86/219 (39%)	67/211 (32%)	24/73 (33%)	5/34 (15%)	23/75 (31%)
Abnormal uvula/ palate	82/219 (37%)	77/231 (33%)	19/70 (27%)	3/34 (9%)	22/75 (29%)
Malar hypoplasia	32/52 (62%)	9/12 (75%)	9/9 (100%)	0/19 (0%)	
Retrognathia	20/40 (50%)			17/41 (41%)	10/75 (13%)
Blue sclerae	16/40 (40%)		0/20 (0%)		5/75 (7%)
Craniosynostosis	32/186 (17%)	20/190 (11%)	3/9 (33%)	0/19 (0%)	
Exotropia	1/12 (8%)	8/79 (10%)	0/9 (0%)		
Velvety skin	11/40 (28%)	9/11 (82%)	29/48 (60%)		7/32 (22%)
Easy bruising		8/12 (67%)	10/28 (36%)	6/19 (32%)	14/75 (19%)
Atrophic scars	33/142 (23%)	68/228 (30%)		2/15 (13%)	
Striae	8/40 (20%)	27/78 (35%)	24/60 (40%)	11/34 (32%)	4/75 (5%)
Umbilical/inguinal hernia	4/12 (33%)	23/90 (26%)	32/87 (37%)	15/34 (44%)	13/75 (17%)
Translucent skin	83/212 (39%)	85/238 (36%)	10/17 (59%)		9/32 (28%)
Dural ectasia	1/11 (9%)	7/18 (39%)	10/21 (48%)	4/34 (12%)	
Bladder/uterine/ rectal prolapse			7/17 (41%)		1/43 (2%)
Varices			18/31 (58%)	1/15 (7%)	3/43 (7%)
Seasonal allergies			10/17 (59%)		

pes planus (24–91%) and scoliosis (33–61%). In a cohort of 28 patients with SMAD3 mutations with a median follow-up of 10 years, the rate of increase in aortic diameter was 0.4 mm per year with the sino-tubular junction being involved most frequently and during follow-up up, 50% of patients required elective root replacement (20).

3.1.4. LDS type 4

Mutations in TGFB2 lead to the development of LDS Type 4. While there were only 24 identified case reports of LDS type 4, the majority (75%) were of high quality (Table 2). These patients demonstrated a high prevalence of: aortic aneurysms, joint laxity, pectus deformities and scoliosis. Amongst cohort studies (Supplementary Table 6), that included between 3 and 19 individuals (21–25), other commonly observed features included: arachnodactyly, pes planus, high-arched palate and umbilical/inguinal hernias (Table 3). The prevalence of aortic aneurysms ranged from 22 to 100% and a history of aortic dissection was reported in 9–11% of cases.

3.1.5. LDS type 5

Mutations in TGFB3 lead to the development of LDS Type 5. There were only six reported individual case reports (Table 2) and two cohort studies (Supplementary Table 7) that included between 32 and 43 individuals (4,26). This cohort demonstrated similar characteristics to other subtypes including: aortic aneurysms, arachnodactyly, pectus deformity, pes planus, hypertelorism, abnormal uvula and joint laxity (Table 3). The prevalence of aortic aneurysms ranged from 14 to 32% and in one cohort a history of aortic dissections was observed in 23% of individuals.

3.2. Cardiovascular involvement

While LDS type 1 and 2 have similar risks of aortic dissection, in LDS type 1 males demonstrated a greater risk of aortic complications compared to females (12,27,28). In addition, aortic emergencies appear to occur at smaller aortic dimension in patients with LDS type 2, who tend to have lower body surface area (12,27,28). In studies with serial follow-up, rates of aortic root dilation ranged from 0.11–0.67 cm/year (13,20,29), with children with LDS type 2 demonstrating the greatest progression of aortic root dilation compared to LDS type 1 and 4 (30). Several studies have also identified a correlation between the presence of craniofacial features (13,14), carotid artery tortuosity (31), vertebral artery tortuosity (32), aortic arch geometry (33), aortic stiffness (34), and mitral annular disjunction (35) with increased aortic risk. Aortic root dilation in children should lead to the suspicion of connective tissues disorders, including LDS. In a cohort of 25 pediatric patients with undiagnosed aortic root dilation, 28% had an underlying undiagnosed connective tissues disease, 5 of which had Marfan syndrome and 1 who had LDS type 3 (36). Non-aortic aneurysms are common (as high as 78% in imaging studies) in LDS, requiring multiple open and endovascular interventions (37). Of note, non-aortic arterial involvement cannot be predicted by aortic involvement and most frequently effects the carotid, subclavian and intracranial arteries (37,38).

A carotid bifurcation angle of greater that 80 degrees (chalice sign) has been demonstrated to have a 67% sensitivity and 82% specificity for LDS (39). Vertebral arterial tortuosity is also commonly observed in patients with LDS (90%), while only observed in 40% of patients with Marfan syndrome (40). The overall prevalence of arterial tortuosity is also likely under reported. In series that only included participants with neuroimaging, arterial tortuosity was observed in 80–100% of patients depending on the vascular territory examined (41–44).

In surgical cohorts, patient with LDS generally demonstrate high rates of aortic reoperation compared to Marfan syndrome and increased risk of post-operative aortic dissections (45–50). However, other cohorts have conversely demonstrated no additional risk of reoperation (51).

Spontaneous coronary artery dissection has been reported in 14 patients with LDS (27,33,43,52–58), however in a cohort of 107 patients

with spontaneous coronary artery dissection who underwent genetic evaluation, only 8% had an underlying connective tissue disease (52).

3.3. Skeletal involvement

Spondylolisthesis and spondylosis is likely underreported, with robust studies demonstrating a combined prevalence of 21% in a cohort of 138 patients, requiring surgery at a median age of 11 years (59). Similarly, in cohort studies of patients with imaging available, scoliosis was present in 46–62% (41,60,61) and cervical vertebrae malformation in 29–76% (61,62). While scoliosis is common in LDS, it lacks specificity for LDS. Of 343 patients with adolescent idiopathic scoliosis, only 2 had undiagnosed LDS type 3 and 1 had Marfan syndrome (63). In a cohort of LDS patients who were reviewed for musculoskeletal involvement, 66% had pectus abnormalities and 17% had talipes equinovarus (club foot). In a cohort of 57 patients with LDS, 33 (58%) patients had reported at least one fracture (64). Of these patients 14 underwent dual-energy x-ray absorption scans that demonstrated that 61–71% had low or very low bone mineral density (64). Overall, patients with LDS have a high burden of musculoskeletal involvement with ~20% requiring surgical intervention, which is frequently complicated and requires additional operations (65).

3.4. Craniofacial involvement

In cohorts of LDS patients who underwent detailed oro-dental examination, most patients have an abnormal palate (85–88%), have retrognathia (83%), dental malocclusion (55–97%) and have enamel defects (55%) which were more severe in LDS type 2 (25,66).

In ophthalmologic studies, hypertelorism was present in 61%, exotropia in 41% and blue sclera in 47%, with LDS type 1 and 2 demonstrating a higher prevalence of blue sclera (67). In contrast to other reports, in an analysis of 25 patients with LDS who also underwent ophthalmologic examination, there was no difference in pupillary distance (objective assessment of hypertelorism) compared to healthy controls (68). However, they do note that males with LDS type 2, demonstrated a trend towards increased pupillary distance that may explain differences between reports. They also note that patients with LDS demonstrated increase myopia, and reduced central corneal thickness.

3.5. Neurological involvement

In a survey study of 67 patients with LDS and their caregivers, neurodevelopmental concerns are believed to be an underrecognized aspect of LDS, with 30% reporting motor delays, feeding issues (41%), hearing problems (31%), poor vision (77%) and weak muscle tone (62%) (69). In an otologic series, patients with LDS across all subtypes demonstrated hearing loss (42%), with predominant conductive hearing loss in LDS type 1 and 2 and sensorineural hearing loss in LDS type 3 and 4 (67).

Dural ectasia while rare in the general population, demonstrates an increased prevalence in patients with connective tissue disorders. The prevalence of dural ectasia in neuroimaging studies has been found to be 40–73%, similar in prevalence and severity to patients with Marfan syndrome (61,70–73).

3.6. Gastrointestinal/genitourinary involvement

Few studies have robustly explored the gastrointestinal manifestations of LDS. In a small survey of 13 patients with LDS, a large proportion describe symptoms of constipation (77%) and diarrhea (46%), which was statistically higher than patients with vascular Ehlers-Danlos syndrome (74). Endoscopy studies of this population is scarce, with a study of four patients in which one was found to have congestive gastropathy and a second was found to have esophageal candidiasis (74). The prevalence of inflammatory bowel disease in LDS (4%) is five times higher than the general population and was frequently refractory to conventional therapies (75). Children with LDS typical have a body mass index significantly below average which can be related to a variety of reasons including repeated surgical interventions, intestinal inflammation and food allergies (76). In a cohort of 182 children with LDS, 6% required a gastrostomy tube which was associated 0.1 increase body mass index z-score per month of tube placement and was not associated with any complications (77).

3.7. Atopic involvement

Early reports did not recognise the atopic effects of TGFB mutations. As TGFB regulates regulatory T cell maturation and immune homeostasis (78), multiple studies have demonstrated the clinical impact of this in patients with LDS. These studies have demonstrated an increased prevalence of asthma (50%), eczema (50%), allergic rhinitis (43%), food allergies (29%) and eosinophilic infiltration of gastrointestinal tract (14%) (76).

3.8. Other

With the wide spectrum of pathologies associated with LDS, patients frequently have a high health burden requiring serial follow-up with multiple healthcare workers. In a survey of 34 patients with LDS, 62% were not working/in-school due to disability and 71% requiring hospital services at least on a yearly basis (79).

3.9. LDS in pregnancy

Previous reviews have been limited to small sample of patients with LDS in pregnancy, limiting their generalisability (80). In case reports of LDS in pregnancy we identified 21 women with LDS who underwent 27 pregnancies (58,81–97). In cohort studies, we identified a further 201 women with LDS who underwent 495 pregnancies (1,12,16,27,46,48,98–101). In total, amongst the 222 women with LDS who underwent 522 pregnancies, 35 (7%) of pregnancies were complicated by at least one complication and included: aortic dissection (4% - of which 10 were Type A, 8 were Type B and 5 were unreported), postpartum hemorrhage ($n = 9$), uterine rupture ($n = 2$), uterine prolapse ($n = 1$), spontaneous coronary artery dissection (n = 1), carotid artery dissection (n = 2), vertebral artery dissection (n = 1) and unexplained sudden death (n = 1). Overall, 4 (1%) deaths were reported during pregnancy or postpartum.

4. Discussion

Although LDS is considered a rare disorder, we have been able to identify 3896 reported cases in the literature. As TGFB-signalling pathways affect multiple organ systems, it is unsurprising that we have observed a wide degree of involvement of the cardiovascular, musculoskeletal, neurological, gastrointestinal systems. Illustrating the prevalence of these phenotypes across the subtypes of LDS demonstrates the wide spectrum of the disease as it pertains to each subtype, allowing clinicians to identifying patients who share multiple attributes of LDS.

Compared to other syndromic inherited aortopathies, LDS demonstrates a similar prevalence of aortic aneurysms (33% in this review), compared to Marfan syndrome (51%), Turner Syndrome (35%) and vascular Ehlers-Danlos (28%) (102,103). However, they generally demonstrate a much higher risk of dissection (11% in this review) compared to Marfan syndrome (0.8–12%), Turner syndrome (1–5%) and vascular Ehlers-Danlos (1–6%) (103). Additionally, dissections occur at a younger age in patients with LDS compared to other hereditary aortopathies (103). Additionally, while patients with LDS demonstrate generalised arterial tortuosity and aneurysms beyond the aorta, they are infrequently observed in Marfan syndrome (104,105). Other

key distinguishing features of LDS to other aortopathies include the absence of ectopia lentis (identified in only 4 cases in our review) and a much higher prevalence of hypertelorism, bifid uvula and cleft palate (106).

Genetic counselling is recommended for all patients with suspected LDS to determine if genetic testing is required (107,108). In addition to confirming the diagnosis, genetic testing guides management, provides prognostic information and informs recurrence risk. In addition, the identification of LDS allows for further screening for silent vascular pathology that may require elective intervention to avoid significant, and at times, catastrophic future complications. Current guidelines recommend lower thresholds for elective intervention on the thoracic aorta, due to the aggressive disease course as well as more frequent imaging monitoring for disease progression (108–110). Furthermore, a positive genetic test has implications for counselling in regards to future pregnancy and complications surrounding this as well as genetic inheritance given the autosomal dominant nature of the syndrome. In cases where the parent of a patient is known or suspected to have LDS, the recurrence risk is 50%. However, when there is a de novo gene mutation due to germline mosaicism, the recurrence risk in subsequent children is estimated to be less than 1% (1).

The major limitations of this study are driven by the quality of reporting in the included studies as well as small sample sizes in individual studies, highlight the need for high-quality, collaborative registries.

5. Conclusion

LDS is a heterogenous multi-system disorder, with many case reports that we identified presenting a focused presentation on a single

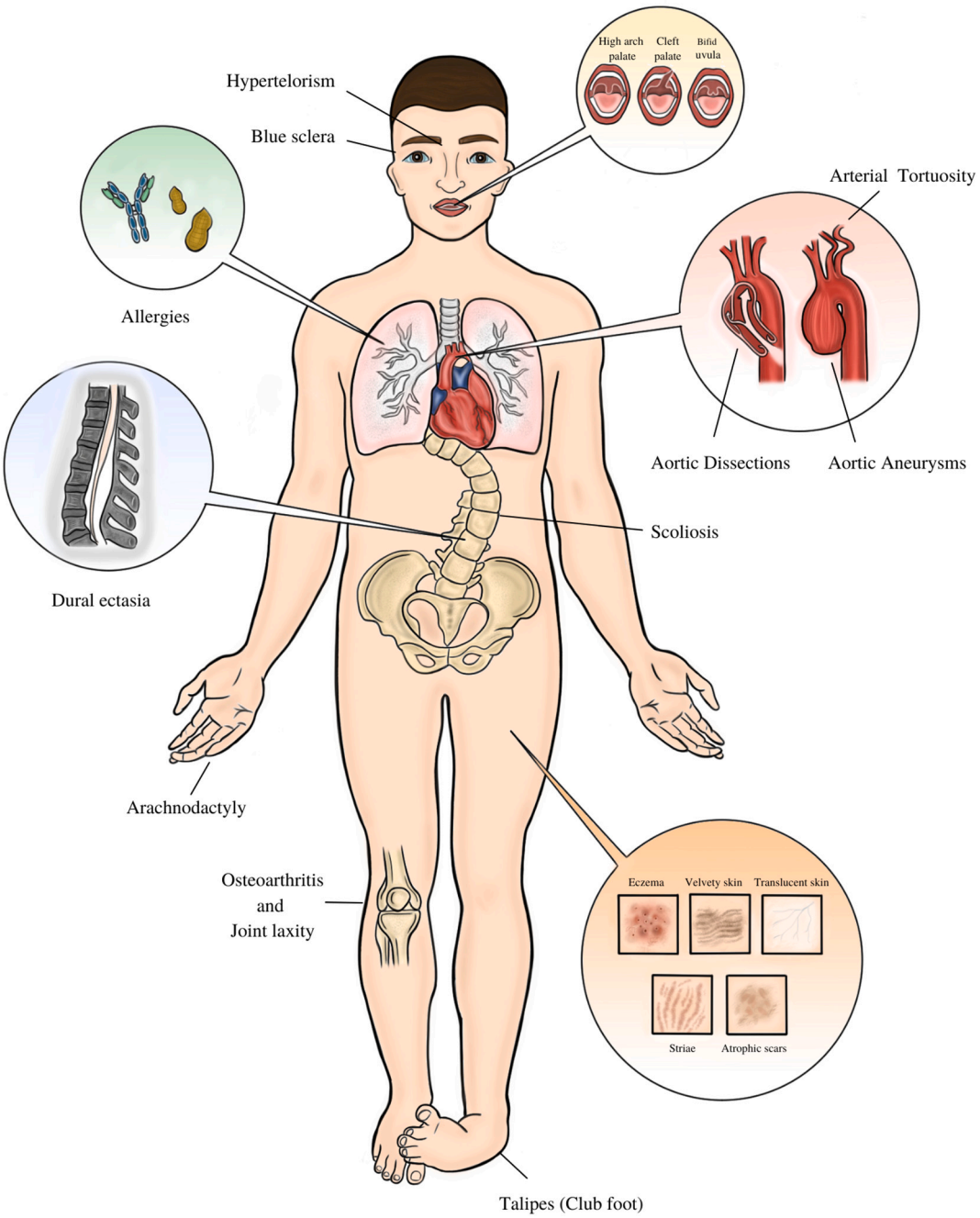

Fig. 1. Spectrum of common features and complications of Loeys Dietz Syndrome.

characteristic or complication of LDS, leading to underreporting of many salient features. This is a major limitation of our review, likely leading to underreporting of characteristics and complications. To address this, large-scale international registries have been established and continue to offer important insights into LDS (12). Until that time, we have utilised the available data to illustrate the wide spectrum of LDS (Fig. 1).

Authors statement

PG - Conceptulization, data curating, formal analysis, methodology, project administration, supervision, writing original draft, review and editting.

RK - conceptulization, data curating, reviewing and editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.05.065.

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