Aortic and vascular involvement in Loeys-Dietz Syndrome. Results from the REPAG registry (Spanish network of genetic aortic diseases).

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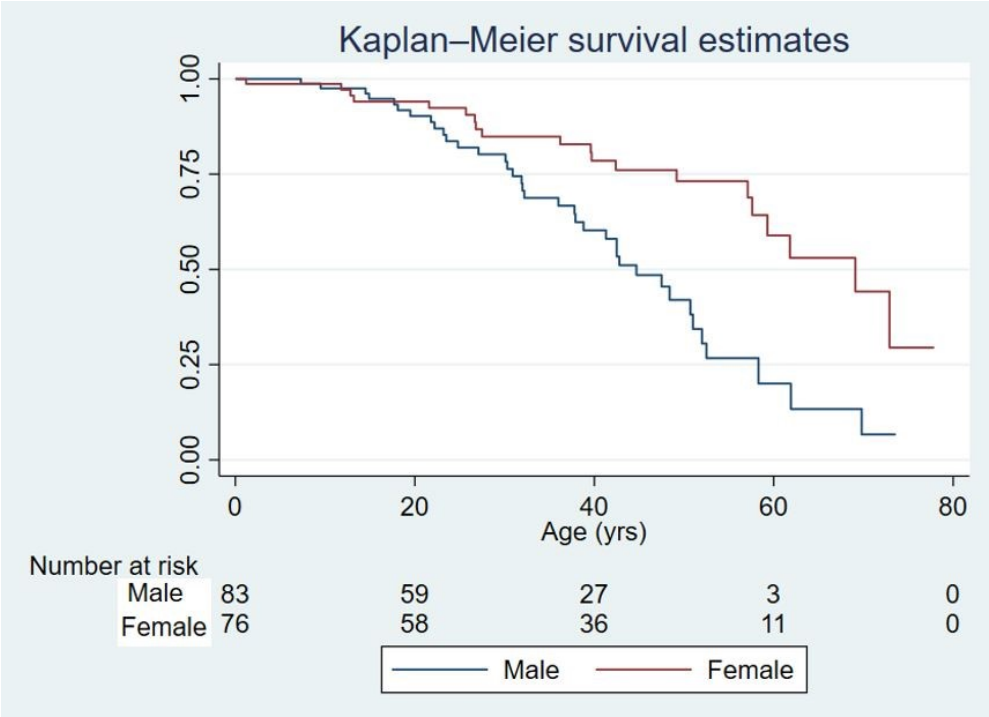
Background LDS is a rare disease due to genetic variants in the TGFB pathway. Limited information is available regarding the overall aortic and vascular outcome of these patients
Purpose: to evaluate aortic and vascular complications of patients with mutations in the TGFB pathway.
Methods: retrospective longitudinal study including patients with (likely) pathogenic (LP/P) variants in the TGFbeta pathway from 10 tertiary centers. Clinical and imaging data were reviewed and data on aortic and vascular outcome included.
Results: A total of 163 patients were included (47.9% women, 38.6% index cases), mean age at first evaluation 32.3±20.4yrs, 27.0% with age <16yrs. 70 TGFBR1, 43 TGFBR2, 29 SMAD3, 9 TGFB2 and 12 TGFB3 (Table1)
During a mean follow-up of 4.7±3.7yrs, 54 (33.1%) patients had at least 1 aortic surgery (max 6). Mean age at first aortic surgery was 37.2±16.8yrs (Range 1.2–72.9). First surgery was elective in 42 (77.8%), and included aortic root or ascending aorta in 40 (95.2%) and isolated descending aorta in 2 (4.8%). Emergent surgery included aortic root or ascending aorta in 11 (92.7%). Ascending aorta-root diameter previous to elective surgery was 48.9±4.9mm (range 41-65). 7 patients died during follow-up (2 intracranial bleeding, 1 SD, 2 aortic ruptures, 1post aortic surgery, 1 non-CV). Furthermore, 19 acute aortic syndromes (AAS) were reported (17 dissections , 2 haematomas) in 18 patients, 10 type A (52.6%). Mean age at first AAS was 42.3±11.1yrs (min 19.7yrs to 62.9yrs)
Median survival free of intervention, dissection or death was 57.1yrs, being worst for men than women (44.7 yrs vs 69.1yrs, p<0.001) (Figure 1), these gender-difference only remained significant in the TGFBR1 and SMAD3 groups (p=0.005 and p=0.008) Regarding aortic branch and intracranial aneurysms, a total of 383 imaging studies of aortic branches and 223 cranial imaging studies were performed during the clinical follow-up. 21 cranial aneurysms and 73 aortic branch aneurisms were reported. 14 (11.5%) patients suffered 19 aneurysms-related events (3 dissections, 3 ruptures, 13 interventions).
CONCLUSIONS
In patients with Loeys-Dietz Syndrome, there's a high prevalence of aortic surgeries and acute aortic events, with high numbers of peripheral and intracranial aneurysms. A worst prognosis in men than in women is observed in TGFBR1 and SMAD3 variants. Thus, specialized clinical and imaging follow-up is crucial in the management of these patients

	Index cases	Elective ascending aortic surgery (mean age)	Acute aortic syndrome (mean age)	Non-aortic aneurysms-related events
TGFBR1, 70 (42.9%)	22 (31.4%)	18, 25.7% 37.6±18.4yrs	7 (10.0%) 44.9±9.4yrs	6 (9.7%)
TGFBR2, 43 (26.4%)	24 (55.8%)	15, 34.9%) 23.0±14.0yrs	5 (11.6%) 31.1±8.1yrs	5 (12.8%)
SMAD3, 29 (17.8%)	8 (12.5%)	6 (20.7%) 46.6±19.5yrs	4 (13.8%) 49.9±11.2yrs	2 (9.52%)
TGFB2, 9 (5.5%)	3 (33.3%)	1 (11.1%) 30.9yrs	0	0
TGFB3, 12 (7.4%)	6 (50%)	1 (8.3%) 37.9yrs	2 (16.7%) 45.4±4.2yrs	1 (14.3%)


Kaplan–Meier survival estimates
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
Age (yrs)
Number at risk
Male 83 59 27 3 0
Female 76 58 36 11 0
Male
Female