

Rates of Cerebrospinal Fluid Leaks in Patients with Marfan Syndrome: A TriNetX Study

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Introduction

- Studies have established a connection between Marfan syndrome and spontaneous cerebrospinal fluid (CSF) leaks, along with other hypermobile connective tissue disorders.
- CSF leaks can lead to spontaneous intracranial hypotension, frequently presenting as an orthostatic headache.
- Despite case reports documenting an association between CSF leaks and Marfan syndrome, the prevalence of spontaneous CSF leaks in the Marfan syndrome population remains unclear.
- The objective of this study is to determine the risk of CSF leak development in patients with Marfan syndrome.

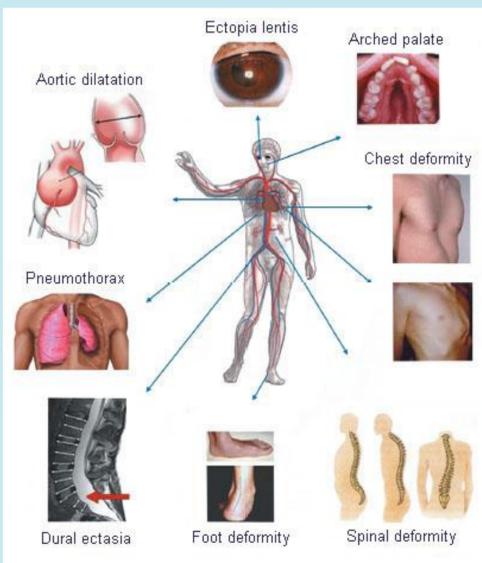


Figure 1. Manifestations of Marfan Syndrome

Methods

- TriNetX Research Network: Retrospective cohort large database study
- Marfan Cohort: Patients diagnosed with Marfan syndrome with a healthcare visit between 2009 and 2015 with ≥ 5 years of follow up
- No-Marfan Cohort: Patients not diagnosed with Marfan syndrome with a healthcare visit between 2009 and 2015 with ≥ 5 years of follow up
- Exclusion criteria: patients who were diagnosed with benign intracranial hypertension, Ehlers-Danlos syndromes, intracranial injury, injury of spinal cord and nerve at all levels, benign/malignant neoplasm of brain/meninges, or fractures of skull and facial bones
- Outcome: Rate of CSF Leaks

Results

Demographics of Marfan v No-Marfan Cohort

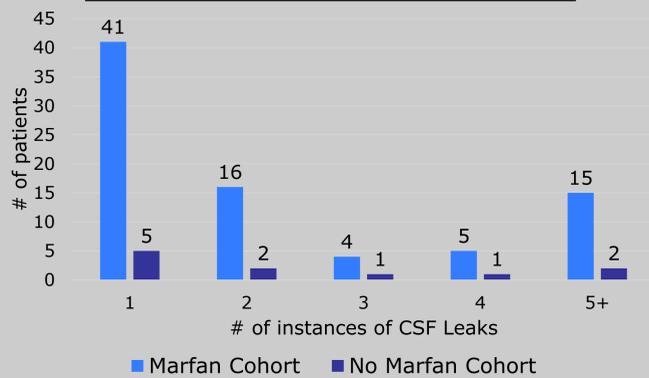
	Marfan Cohort	No-Marfan Cohort
Total cohort (n)	15,050	40,797,299
Age @ index (years)	25.3 \pm 19.3	37.3 \pm 23.2
Sex		
Male, % (n)	8,469 (56.27%)	17,146,828 (42.03%)
Female, % (n)	6,404 (42.55%)	22,745,731 (55.75%)
Ethnicity		
Hispanic or Latino	1,435 (9.53%)	3,786,938 (9.28%)
Not Hispanic or Latino	11,248 (74.74%)	25,176,902 (61.71%)
Race		
White	10,459 (69.5%)	24,280,913 (59.51%)
Black	1,689 (11.22%)	5,661,981 (13.88%)
Asian	656 (4.36%)	2,156,938 (5.29%)

Results (cont.)

Risk of CSF Leak Development		
Before propensity score matching		
	Marfan Cohort	No-Marfan Cohort
# of patients who developed CSF leaks	81	25,378
% of patients who developed CSF leaks	0.538%	0.062%
After propensity score matching		
	Marfan Cohort	No-Marfan Cohort
# of patients who developed CSF leaks	81	11
% of patients who developed CSF leaks	0.539%	0.073%

- Before propensity score matching, patients with Marfan syndrome demonstrated an 8.7-fold increased risk of CSF leak development compared to controls (RR 8.65, 95% CI 6.96-10.76, $p < 0.0001$).
- After propensity score matching for age, patients with Marfan syndrome demonstrated a 7.4-fold increased risk of CSF leak development compared to controls (RR 7.37, 95% CI 3.92-13.82, $p < 0.0001$).
- Generally, when Marfan patients have a CSF leak, they have 1 instance.
- More patients in the Marfan cohort have increased number of instances of CSF leaks compared to the counterpart No-Marfan cohort
- 15 Marfan patients have 5 or more CSF leaks compared to 2 in the No-Marfan cohort.

Number of Instances of CSF Leaks in Marfan Cohort v No-Marfan Cohort



Discussion

- Patients with Marfan syndrome show a significantly increased likelihood of experiencing CSF leaks relative to the general population, with a 7 to 8-fold elevated risk that reinforces the proposed link between the dural weakness in Marfan syndrome and spontaneous CSF leakage.
- The underlying pathophysiology involves abnormal fibrillin-1 protein deposition that compromises the integrity of connective tissue structures throughout the neuraxis.
- This association is attributed to dural ectasia (stretching of the dura), which has a high prevalence in Marfan patients and creates structural weakness that may predispose to CSF leakage through weakened dural membranes and development of meningeal diverticula.
- These findings highlight the importance of incorporating clinical suspicion for CSF leaks in routine monitoring and management protocols for this patient population.



Figure 3. Sagittal T2-weighted image of the lumbosacral spine showing diffuse dural ectasia.

Conclusions

- This study, the largest of its kind to date, demonstrates a notable association between Marfan syndrome and CSF leak development
- Clinicians should maintain heightened awareness for symptoms of intracranial hypotension in Marfan patients, potentially leading to earlier diagnosis and treatment of serious complications.

References

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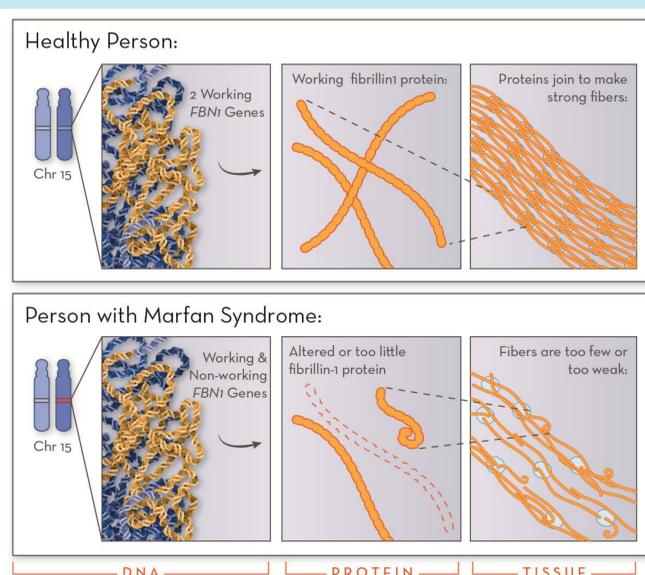


Figure 2. Molecular Basis of Marfan Syndrome