Variations in age of onset and long-term treatment outcomes in men and women with Sorsby's dystrophy.

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INTRODUCTION

- Sorsby's fundus dystrophy is a bilateral uncommon late onset autosomal dominant condition causing severe loss of vision in adults. It typically presents with sudden loss of central vision in one eye followed by the second eye, weeks and months later.
- Clinically it is characterised by sudden onset sub-foveal choroidal neovascular membranes (CNVM), retinal haemorrhages followed by retinal pigment epithelial proliferation and subretinal fibrosis.
- Left untreated, the disease usually progresses rapidly due to aggressive, recurrent CNVM.

The disease is caused by the pathogenic TIMP3 missense variant gene 'Ser204Cys' (formerly known as 'Ser181Cys') at Chr 22

METHODS

- A retrospective study of 10 eyes of 5 patients presented to our centre over a period of 19 years (2005-2024).
- All patients were symptomatic and presented with CNVM in at least one eye.
- All patients had OCT / OCTA scans, Fundus autofluorescence, Fundus fluorescein angiography and genetic testing (where relevant) to confirm the diagnosis.
- All tested were positive for TIMP 3 missense mutation chromosome 22.
- The treatment regimes included oral steroids, sub-tenon steroid injections, PDT and intravitreal anti-VEGF injections.

Table 1

Name	Age @ presentation	Sex	Visual acuity @ presentation		Final visual acuity		Treatments	Years of Follow up	Smoker
			Right	left	Right	Left			
1 HG	35	F	6/6	6/9	6/6	3/60	Laser x 3 Left Avastin x3 left Lucentis x9 Right	20	Yes
2 JN	45	M	6/6	6/9	CF	1/60	Lucentis Right 30 Left 13	11	Yes
3 GN	46	M	HM	CF	HM	CF	Both eyes Laser x10	17	Yes
4 HG	25	F	6/5	6/12	6/5	6/6	Oral steroids	4	No
5. ME	35	F	6/18	6/18	CF	6/60	Both eyes Lucentis x 3 PDT x2	20	No

Patient 1:

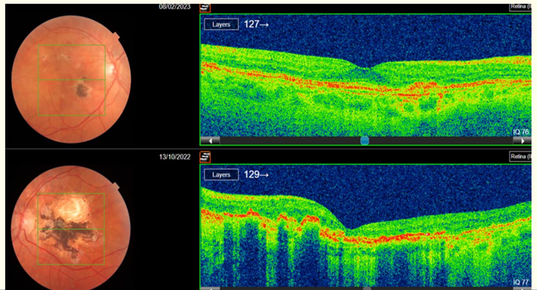
Patient presented with left extrafoveal CNV with was successfully treated with confluent laser (VA 6/6) but suffered with sub foveal recurrence 2 years later which left her with fibrous scar.

She received 3 intravitreal Avastin injections into her left eye.

She was positive TIMP3 missense variant at Chr 22

Four years after the first eye involvement she came with a CNVM in her RE for which received only 9 injections over a period next 16 years.

VA on her last visit to clinic are 6/6 in the right and 3/60 in her left.

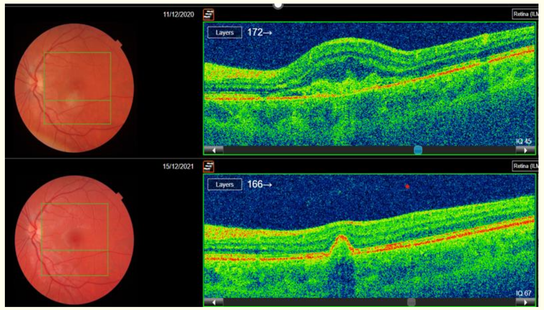


Patient 4:

Presented in December 2020 with juxta-foveal CNVM with blurring of vision and a paracentral scotoma. OCT/ OCTA/ FFA demonstrated a small CNVM. She was positive TIMP3 missense variant at Chr 22. Her mother was diagnosed with Sorsby's dystrophy 8 years ago

She refused any intravitreal injection in spite of the significant risk to her central vision therefore she was treated with oral prednisolone which successfully resolved the CNVM within 4 weeks.

3.5 years later her visual acuity remains good at 6/6 in the affected eye. No signs of any recurrent / new CNVM seen in either eye.



RESULTS

- Age: Age at presentation ranged from 25 – 46 years.
- Sex: 3 females and 2 males from 2 unrelated families.
- Follow up period: Ranged from 4 to 20 years with average follow up period of 14.7 years.
- Three eyes received Argon laser, 2 received PDT, one oral steroid, 6 eyes had intravitreal anti-VEGF injections and 3 eyes had combination treatments.
- Argon laser treatment proved to be least effective with high rate of recurrences of choroidal neovascular membranes with subsequent loss of central vision.
- Anti-VEGF treatments were universally effective.
- Final Visual acuity varied from HM to 6/6
- Both male patients deteriorated rapidly, lost vision in both eyes and were registered blind.

CONCLUSION

- **In-spite of the common gene defect, the age of onset of sight threatening disease seems to differ in men and women and the final visual outcomes also seem to vary widely (table 1). These discrepancies were not reported previously. The disease manifested on average 10 years earlier in females than their male counterparts and females achieved better visual outcomes. Females also required fewer intravitreal injections.**
- **Males also suffered severe form of maculopathy and lost all useful vision and were registered blind. Smokers did much worse and treatments proved less effective.**
- **The advent of anti-VEGF treatments has improved the overall outcomes, but the females seem to do much better.**
- **It may be advisable to screen gene positive male relatives more frequently.**