



COMMENT



Straatsma plus syndrome: beyond the classic triad

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Straatsma syndrome is a complex and exceptionally rare ophthalmic entity defined by the classical clinical triad of myelinated retinal nerve fibres (MRNFL), ipsilateral high myopia, and profound amblyopia. The existing literature is limited primarily to isolated case reports and small case series. Most cases are unilateral and are associated with markedly reduced visual acuity. Amblyopia in Straatsma syndrome is typically refractory to treatment and demonstrates a poor response to both refractive correction and occlusion therapy [1].

In a cohort of 39 patients, mean age at diagnosis was 5.1 ± 4.8 years (range, 6–28); visual acuity, 1.1 ± 0.5 logMAR; mean spherical equivalent refractive error (SER), -8.4 ± 5.3 D (64% of eyes ≤ -6.00 D); and strabismus was present in 62% of patients (62.5% exotropia). Among 30 eyes (76.9%) receiving amblyopia therapy (mean duration, 2.4 ± 1.6 years), mean final visual acuity was 0.9 ± 0.7 logMAR (mean improvement, 13.5 ± 4.7 letters); however, 51% remained worse than 6/9 (> 0.18 logMAR) [1].

Driven by distal migration of myelin-producing oligodendrocyte progenitor cells (OPCs) from the lateral geniculate nucleus, RNFL myelination occurs due to ectopic migration of OPCs to retinal ganglion cells, driven by the distal migration of myelin-producing OPCs from the lateral geniculate nucleus. This can occur due to transient impairment of the physical barrier function of the lamina cribrosa or when OPC migration precedes the complete development of the lamina cribrosa [1]. Three distinct patterns have been described, all characterised by myelination continuous with the optic disc: Type 1 is observed in the superior retina; Type 2, the most common, involves both the superior and inferior retinæ; and Type 3 is observed in the inferior retina [2]. Other patterns of myelination have been described, including inferior myelination without continuation to the optic disc or isolated MRNFL elsewhere and isolated macular MRNFL [1, 2].

Retinal image blurring from extensive MRNFL is presumably the primary mechanism underlying high myopia in these patients. While a few studies have reported hyperopia with MRNFL, form-deprivation myopia appears to be the primary determinant of exaggerated ocular growth in eyes with extensive MRNFL, and a paradoxical ocular response to form deprivation has been proposed [3]. Although a recent study of 19 eyes found no relationship between the MRNFL area and the degree of myopia [2], a careful review of published data suggests that a larger MRNFL area, as well as density, may be associated with higher degrees of myopia [4]. It remains to be determined, using larger samples, whether a larger MRNFL area is directly associated with more severe myopia or if both conditions emerge from aberrant ocular development during the gestational and early postnatal periods.

Profound treatment-refractory amblyopia observed in Straatsma syndrome arises from a complex multifactorial pathophysiology. Key amblyogenic factors include anisometropia and severe form deprivation, resulting from dense MRNFL and blurred retinal images during early infancy, frequently complicated by concurrent strabismus [1, 2].

PROPOSED CLASSIFICATION SCHEME

Beyond the classic Straatsma triad, several associated ocular findings have been reported, which can be broadly categorised as additional primary features (congenital or developmental in origin) and secondary features (complications arising from the classic triad). Primary features include foveal and optic nerve hypoplasia, persistent foetal vasculature (PFV), dome-shaped maculopathy, congenital cataracts, and heterochromia iridum [1, 2, 4–6]. While driven by distinct pathophysiological mechanisms, these primary features, including abnormal myelination, dysplastic optic nerves, foveal hypoplasia, PFV, and heterochromia iridum, collectively support an early insult to neuroectodermal neural crest cell migration [1, 7–9]. Consequently, these features of congenital/developmental origin were considered additional primary features. Conversely, strabismus, nystagmus, tilted optic discs, and acquired cataracts manifest as complications of the spectrum and are thus categorised as secondary features [1, 2]. An anomalous vitreoretinal interface, characterised by abnormal adhesions overlying the MRNFL areas and vitreoretinal traction, significantly increases the risk of retinal detachment and macular hole formation in highly myopic eyes with Straatsma syndrome [1, 2]. As such, all these anomalies and their resulting manifestations are considered as secondary features (Table 1).

Based on these observations, we propose a modified classification for cases presenting with features beyond the classic triad, as follows:

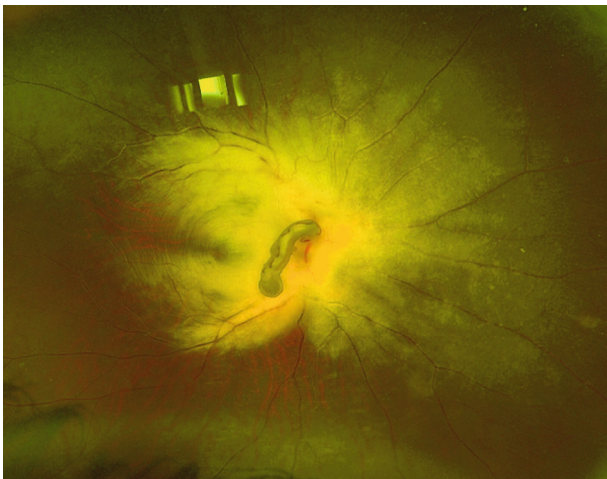
- Classic Straatsma syndrome: MRNFL + myopia + amblyopia +/- secondary feature(s).
- Straatsma plus syndrome: Classic Straatsma features + at least one additional primary feature +/- secondary feature(s).
- Inverse Straatsma syndrome: MRNFL, hyperopia + amblyopia +/- secondary feature(s).

The revised classification defines the Straatsma syndrome spectrum solely based on congenital clinical features. Figure 1 shows a case of Straatsma plus syndrome with PFV.

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Table 1. Additional features of Straatsma syndrome.

Primary features ^a	Secondary features ^b
Heterochromia iridium [10]	Acquired cataract [1]
Congenital cataract [4]	Tilted disc, peripapillary atrophy [1]
Persistent foetal vasculature [6, 11]	Posterior staphyloma [1]
Optic nerve hypoplasia [4, 5, 12]	Retinal detachment, macular hole [13]
Foveal hypoplasia [12]	Ellipsoid zone disruption
	Dome-shaped macula [14]
	Nystagmus [15]

^aRequired for Straatsma plus syndrome.^bNot required for Straatsma plus syndrome.**Fig. 1** Persistent fetal vasculature in a case of Straatsma plus syndrome.

Given that the spectrum stems from aberrant prenatal ocular development, only the features of developmental origin and the classic triad are required for the diagnosis of Straatsma plus syndrome. Whereas secondary features are excluded to avoid complexity. While highly probable, it is unclear if Straatsma plus syndrome carries a poorer prognosis than the classic phenotype.

A detailed discussion of the shared etiopathogenesis of additional features of Straatsma plus syndrome is beyond the scope of this article; yet, converging developmental pathways may plausibly explain the co-occurrence of MRNFL, PFV, and high myopia. Transient dysfunction of the lamina cribrosa or spatial imbalance of OPC migration and lamina cribrosa development may permit ectopic migration of OPCs into the retina, contributing to ectopic retinal nerve fibre layer myelination. Dysregulation of platelet-derived growth factor A signaling, critical for astrocyte and oligodendrocyte precursor cell proliferation and migration, may further disrupt retinal vascular development and myelination [1, 8, 9]. In parallel, Wnt signalling is central to retinal angiogenesis and oligodendrocyte differentiation; its perturbation may impair regression of hyaloid vasculature and alter myelination cues [9]. Axon guidance pathways, including semaphorin and ephrin signalling, coordinate vascular patterning and axon myelination boundaries; emerging evidence suggests ephrin-B signalling contributes to PFV phenotypes [7, 9]. Despite these biologically plausible links, the rarity of this spectrum limits definitive conclusions, and its precise pathophysiological basis remains poorly understood.

Briefly, the revised classification system establishes a foundation for precise clinical phenotyping of Straatsma syndrome. Categorising phenotypes into classic, inverse, and plus types will ensure consistent documentation and reporting of future research.

DATA AVAILABILITY

All data generated or analysed during this study are included in this published article.

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AUTHOR CONTRIBUTIONS

HAK: Conceptualisation, Methodology, Formal analysis, Data Curation, Writing—Original Draft. ZA: Conceptualisation, Data curation, Validation, Writing—Review and Editing. NGS: Data curation, Validation, Writing—Review and Editing. MAS: Validation, Writing—Review and Editing.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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