

Myopia and amblyopia are common diagnoses in pediatric ophthalmology practice. When should you suspect more?

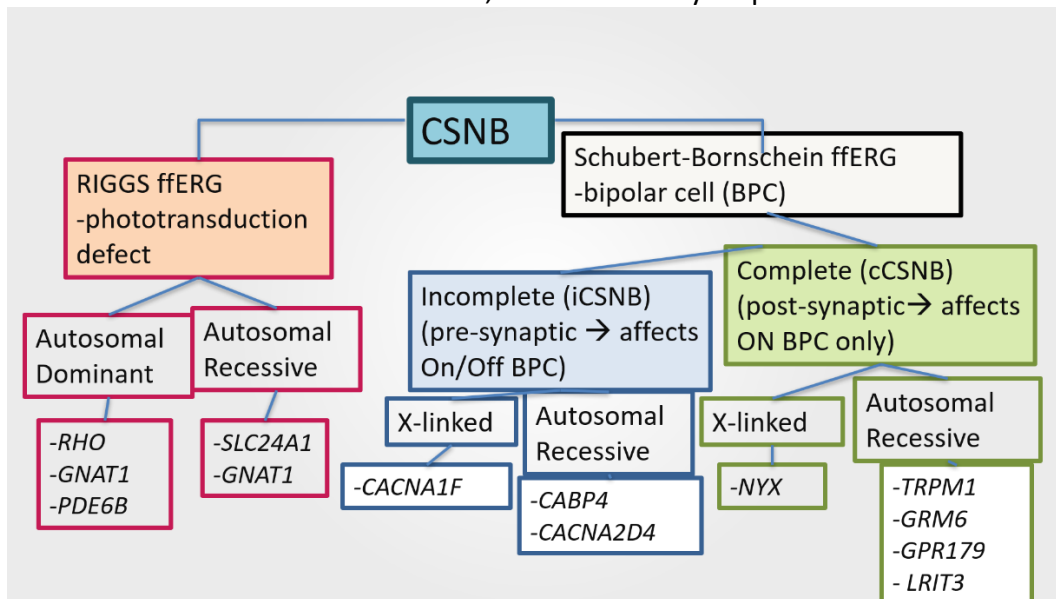
Myopia and amblyopia are among the most common conditions in pediatric ophthalmology practice. While these diagnoses are relatively common and typically manageable, knowing when to suspect underlying genetic disorders contributing to myopia or masquerading as amblyopia is essential.

In this workshop, we present and discuss five clinical cases in which myopia and amblyopia were the presenting signs of a more serious condition. Each example represents a specific class of disorders that presents with juvenile myopia or may masquerade as amblyopia.

Congenital stationary night blindness (CSNB)

CSNB represents a group of diseases that have in common congenital nystagmus, nonprogressive nyctalopia, and abnormal full-field ERG.

- The condition is estimated to affect around 1 in 5,000 to 1 in 25,000 people worldwide.
- The pathology in CSNB affects either bipolar cells or photoreceptor synapses - see diagram
- Electronegative ERG is characteristic (with selective loss of the b wave and rod dysfunction).
- Juvenile onset, high myopia, is a common feature of CSNB. Multiple genes are associated with the disease; high myopia is often associated with X-linked *CACNA1F*, *NYX*, and autosomal recessive *TRPM1*.
- Nyctalopia is not always obvious or present. Infantile-onset nystagmus might improve or resolve over time. In addition, strabismus may be present.



Juvenile glaucoma associated with Singleton-Merten syndrome (SGMRT)

SGMRT is a rare, autosomal dominant inherited condition. *DDX58* (*DExD/H-box helicase 58*) and *IFIH1* (*interferon-induced with helicase C domain 1*) have been implicated in this condition. Ocular features of SGMRT include juvenile glaucoma, cataracts, **juvenile progressive high myopia**, and corneal abnormalities. Juvenile glaucoma is associated with very high intraocular pressure and can be particularly severe and difficult to manage. In addition to ocular features, the systemic features may include:

- Cardiovascular abnormalities: aortic and mitral valve calcification, arterial calcification, and aneurysms.
- Skeletal abnormalities: bone loss, particularly in the jaw and hands, scoliosis, osteoporosis, and joint hypermobility
- Dental abnormalities: premature tooth loss, delayed tooth eruption, and dental root abnormalities.
- Immune system abnormalities: recurrent infections or autoimmune disorders.

The severity and presentation of SGMRT can vary widely among individuals, even within the same family. The mechanism of developing glaucoma in SGMRT is not clearly determined, but it is the most penetrant feature of *DDX58*-related disease (more than 92%) and the leading cause of visual impairment.

Elevated intraocular pressure associated with juvenile glaucoma has been suggested to cause the eye to stretch and elongate, leading to the development or progression of axial myopia. It has also been suggested that biomechanical stresses induced by the increased axial length of the globe are implicated in the development of glaucoma in myopic eyes. The optic disc morphological changes (tilted disc) seen in myopic eyes can cause difficulties in diagnosing and monitoring glaucoma and render myopic eyes more susceptible to damage from increased IOP. These considerations make early diagnosis and treatment of glaucoma challenging in young children.

Marfan syndrome

Marfan syndrome is an autosomal dominant inherited connective tissue disorder caused by pathogenic variants in the *FBN1* gene, which encodes a protein called fibrillin-1. The common features of Marfan syndrome include:

- Skeletal abnormalities: long limbs and fingers, a tall and thin build, and a curved spine, joint hypermobility, which can lead to joint pain and dislocations.
- Ocular abnormalities: iridodonesis, phakodonesis, lens dislocation, **myopia**, glaucoma, strabismus, amblyopia, and cataracts. Myopia can be either axial or refractive, the latter resulting from lens subluxation or dislocation.
- Cardiovascular abnormalities: dilating of the aorta, which can lead to aortic dissection or aneurysm, mitral valve prolapse, which can lead to heart failure.
- Other features: stretch marks, hernias, and lung problems such as spontaneous pneumothorax.

The severity of Marfan syndrome can vary widely between individuals, even within the same family. There is no cure for Marfan syndrome, but early diagnosis and management can help to improve quality of life and prevent potentially life-threatening complications.

Stargardt disease

Stargardt disease is most commonly caused by bi-allelic pathogenic variants in the autosomal recessive *ABCA4* gene. The prevalence of Stargardt disease is estimated to be approximately 1 in 6500 individuals worldwide, with approximately 1.4 million individuals affected worldwide. The *ABCA4* protein is involved in transporting toxic waste products out of the retina, preventing the accumulation of these compounds that can cause damage to photoreceptors and retinal pigment epithelium. The condition typically manifests in childhood or adolescence with blurred or distorted central vision, difficulty reading or recognizing faces, and sensitivity to bright light. Visual symptoms/decreased acuity often precede fundus findings in children:

- 24% of children may have a normal-appearing fundus
- 30% of children do not demonstrate classic "pisciform" flecks
- When fundus abnormalities are not apparent, the disease can be misdiagnosed as functional/nonorganic or bilateral **amblyopia**
- Visual loss can be asymmetric but most commonly binocular. When associated with refractive errors and strabismus, Stargardt disease can masquerade as **amblyopia**.

The most helpful test for evaluation is macula OCT

- ELM thickening (earliest sign) on SD-OCT
- Loss of ellipsoid zone and outer retina
- May spare fovea or target fovea
- May have subfoveal optically empty gap (also seen in achromatopsia, laser injury, and occult macular dystrophy)

Fundus autofluorescence:

- Peripapillary sparing, bullseye maculopathy, flecks

Electrophysiology:

- Can be normal, can be electronegative, can have reduced photopic response, or reduced scotopic and photopic responses in late stages

Perimetry

- Central or cecocentral scotoma with peripheral preservation in most cases

NF1 with optic pathway glioma

Neurofibromatosis type 1 (NF1) is an autosomal dominant inherited disorder. It is caused by pathogenic variants in the *NF1* gene. One of the manifestations of NF1 is optic pathway glioma (affecting the optic nerve, chiasm, or tract).

- The most common ocular feature is Lisch nodules on the iris. These nevus-type lesions are round, slightly elevated, and darker than light irises but lighter than dark brown ones. They accumulate over time, and about 80% of patients with NF1 have some Lisch

nodules by the age of 8-10 years. Lisch nodules are helpful for diagnosis but do not affect vision. Slit lamp evaluation is needed to rule out Lisch nodules.

- Most optic pathway gliomas develop in childhood (before age 10), with the peak of incidence around age 4. Approximately 15-20% of individuals with NF1 will develop an optic pathway glioma. It is estimated that 30% of affected individuals will have a permanent visual impairment in one eye, and 10% will have some degree of permanent visual impairment in both eyes.
- The natural history of optic pathway glioma can vary widely between individuals, with some tumors growing slowly and causing few symptoms. In contrast, others may grow rapidly and cause vision loss or other neurological deficits. Optic pathway gliomas can cause various visual symptoms, including decreased vision, afferent pupillary defects, abnormal eye movements, and visual field defects. In some cases, optic pathway gliomas may cause no symptoms and are discovered incidentally in imaging studies.
- When optic pathway gliomas are asymmetric or unilateral, and the diagnosis of NF1 is unclear, they might be misdiagnosed as **amblyopia**.
- In 1997, an NF1 optic pathway glioma task force performed an extensive literature review and recommended that screening of asymptomatic patients should consist of serial ophthalmology examinations by a pediatric ophthalmologist or neuro-ophthalmologist familiar with NF1. An updated review in 2007 recommended comprehensive eye examinations every year up to the age of 8, followed by examinations every 2 years until the age of 18. Because preverbal children may not show early signs of mildly asymmetric vision, baseline brain MRI may be considered if suspicion is high and examination is difficult.

Key points:

While most cases of childhood myopia are considered "simple myopia" and have a relatively benign course, certain features may suggest an underlying genetic disorder.

- **Early onset:** Myopia that presents in early childhood, particularly before age six, may indicate a genetic disorder. Examples include connective tissue disorders (Stickler Syndrome, Marfan, Knobloch, Wagner syndrome, etc), inherited retinal disorders including CSNB, familial vitreoretinopathies, and congenital and juvenile glaucoma and Retinopathy of Prematurity.
- **High myopia:** Myopia that is severe (high) at onset or rapidly progressive may also be associated with underlying genetic disorders. Examples include connective tissue disorders (Stickler's, Marfan, Wagner syndrome, etc), retinal dystrophies (achromatopsia, blue cone monochromacy, Donnai Barrow syndrome, *RPE65* associated LCA, etc) and retinopathy of prematurity.

As with myopia, certain features of amblyopia may suggest an underlying genetic disorder.

- **Severe:** Amblyopia that is more severe than expected for the risk factor may indicate an underlying disorder. Examples include optic nerve hypoplasia or atrophy, compressive optic neuropathies.
- **Refractive to treatment:** Amblyopia nonresponding to therapy as expected may indicate an underlying disorder. Examples include: retinal dystrophies, LHON, DOA
- **Bilateral:** high refractive errors and bilateral deprivation can lead to bilateral amblyopia. Bilateral amblyopia may suggest an underlying genetic disorder causing the high refractive error or the deprivation versus causing the inadequate response to therapy. Examples include: oculocutaneous albinism associated with high hyperopia, congenital cataracts associated with systemic conditions (*PAX6*-related disorders, etc)

Family history, review of systems, complete physical exam, and a high suspicion and awareness can help in initiating the workup and establishing the diagnosis

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