



Bilateral visual loss, behavioral changes, and overlooking in a young child with stargardt disease: Neurodiagnostic considerations

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ABSTRACT

Purpose: To illustrate the potential diagnostic confusion between Batten disease and Stargardt disease created by associated signs and symptoms.

Observations: A six-year-old girl with vision loss and prominent behavioral changes and overlooking was presumptively diagnosed as having the Batten disease form of neuronal ceroid lipofuscinosis. However, genetic testing confirmed the diagnosis of Stargardt disease.

Conclusions and importance: Behavioral changes and overlooking can accompany the devastating central visual loss of Stargardt disease. In the absence of objective neurologic findings, these features need not signify a potentially life-threatening disease.

1. Introduction

A six-year-old girl was referred for decreased vision and behavioral changes. She had learned to read books before kindergarten but could no longer read by the first grade. Over the past six months, she had become increasingly emotional, anxious, frustrated, with difficulty concentrating on simple tasks. She cried at night, became “more clingy,” and had recently failed a vision screening examination at school. There was no history of myoclonus, seizures or other neurologic dysfunction, and no family history of visual loss in childhood.

On examination, she was alert and conversant. Visual acuity was 20/200 OU, and she could identify only 1 of 14 Ishihara color plates with either eye. She had brisk pupillary responses with no strabismus, nystagmus, photophobia, or paradoxical pupillary constriction to darkness. She displayed a prominent overlooking phenomenon, in which she would gaze above objects of interest (Fig. 1). Results of slit lamp biomicroscopy and tonometry were normal. Optic disc examination showed retinal arteriolar narrowing without optic atrophy (Fig. 2). Retinal examination showed symmetrical a bull’s eye lesions, with oval areas of macular hypopigmentation surrounding an areas of foveal hyperpigmentation (Fig. 2). Optical coherence tomography (OCT) showed macular photoreceptor loss with degeneration within the ellipsoid zone and multiple hyperreflective granular deposits (Fig. 3).

Based on the prominent behavioral symptomatology and the finding

of overlooking, the patient’s mother was informed of the potential diagnosis of Batten disease and its dire implications. However, the results of neurologic examination and magnetic resonance imaging were normal. Genetic testing was negative for all mutations known to cause neuronal ceroid lipofuscinosis, but whole exome sequencing showed compound heterozygosity for 2 pathogenic variants in the *ABCA4* gene (c.3007 C > T p.Q1003X and c768 G > T PV256 =) that established the diagnosis of Stargardt disease.

2. Discussion

In 1980, Spalton et al. first described “overlooking” as a sign of Batten disease.¹ The clinical presentation of rapid bilateral visual loss, behavioral changes, and “overlooking” (eccentric fixation above the area of interest) is highly suggestive of juvenile neuronal ceroid lipofuscinosis (JNCL) or Batten disease,¹ a neurodegenerative disorder caused by mutations in the *CLN3* gene that disrupt lysosomal storage.^{2–4} Batten disease is characterized by the onset of visual loss and between the ages of 4 and 10 years of age. Retinal examination may show macular pigmentary changes, bull’s eye maculopathy, optic atrophy, and retinal arteriolar attenuation, and peripheral pigmentary or atrophic changes.¹ OCT shows severe outer retinal layer loss with macular nerve fiber layer and ganglion cell attrition.⁶ MR imaging shows focal regions of abnormal white matter signal intensity throughout the brain.⁷

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Fig. 1. Facial photo (left) showing overlooking.

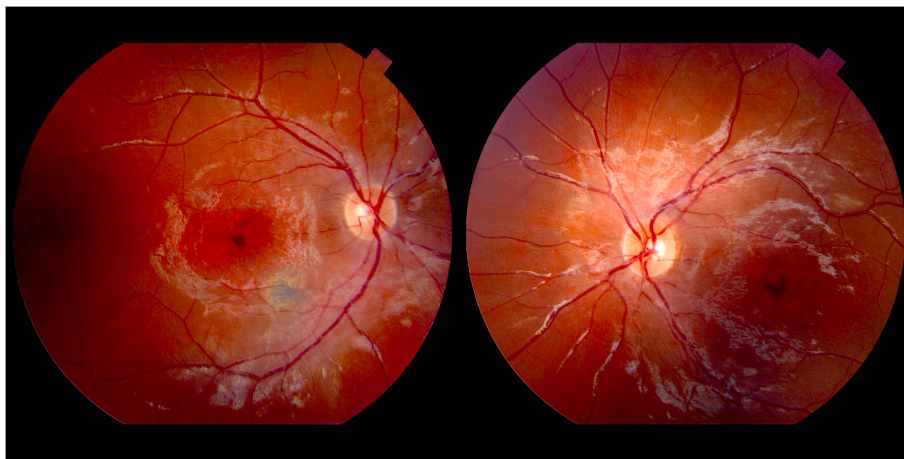


Fig. 2. Retinal photo (right) shows retinal arteriolar narrowing with symmetrical oval areas of macular hypopigmentation surrounding an area of foveal hyperpigmentation (bull's eye lesion).

Neuropathologically, juvenile NCL is associated with widespread neuronal degeneration, causing retinal atrophy and massive loss of brain substance late in the disease, and accumulation of intracellular lipopigments.⁵ Electroretinography shows a markedly reduced b:a ratio in the dark adapted bright flash ERG early in the course, which becomes nonrecordable after about 2 years.^{2,6} Visual problems are often accompanied by prominent neurobehavioral changes (disordered sleep, obsessive-compulsive behaviors, angry outbursts, anxiety and depression), and followed by rapid neurologic deterioration (seizures, parkinsonism, dysarthria).^{1-4,8} There is no known treatment and the condition is ultimately fatal.

Despite the sentinel behavioral changes in this child, her neurologic

and neuroimaging studies were normal, which led us to consider the diagnosis of Stargardt disease, a common inherited retinal degeneration characterized by loss of central vision in both eyes. Although the visual loss usually occurs over years, some patients with Stargardt disease experience loss of vision over weeks to months.⁹ Mutations in the *ABCA4* gene, which encodes a photoreceptor-specific binding protein, are responsible for most cases of Stargardt disease. The onset of Stargardt disease in early childhood may portend more severe visual loss with generalized visual dysfunction.¹⁰ The differential diagnosis includes ciliopathies such as Bardet-Biedl syndrome, cones dystrophies, and cone-rod dystrophies, all of which may cause overlooking due to eccentric fixation,¹¹ and be accompanied by behavioral changes due to

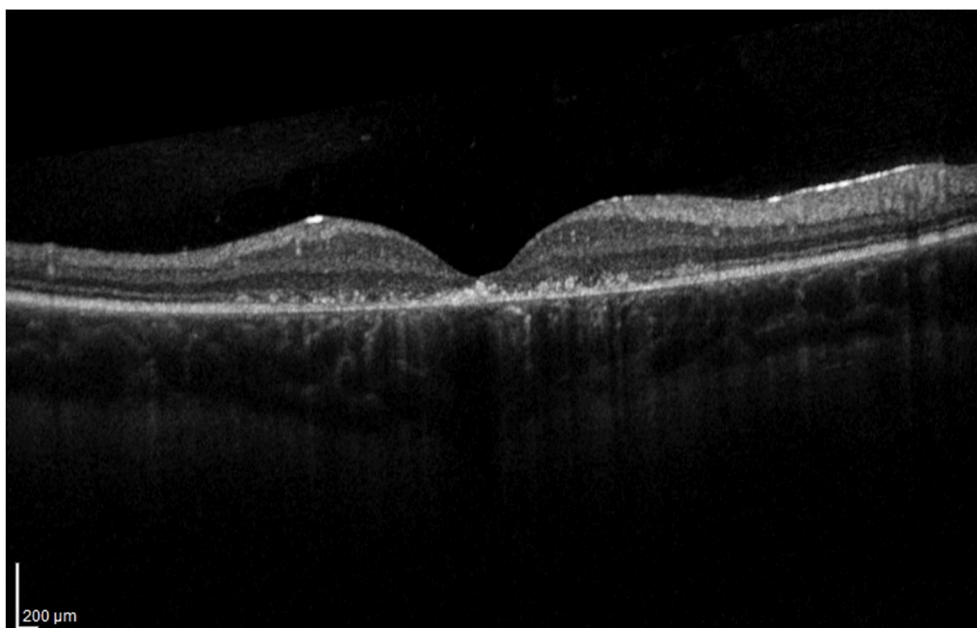


Fig. 3. Macular Spectralis OCT shows photoreceptor loss with outer retinal degeneration and multiple hyperreflective granular deposits.

the stress of losing vision rapidly without support due to lack of diagnosis. A recent report documented a child with apparent Stargardt disease who, on genetic testing, was found to have Batten disease.¹⁰ Conversely, we have examined children with Stargardt disease and prominent behavioral changes that initially raised the question of Batten disease.

Genetic testing is now considered to be the diagnostic test of choice for both Stargardt and Batten disease. Panels covering multiple genes associated with central vision loss in children are readily available. Electroretinography would show diminished B waves in Batten disease and is often normal in Stargardt disease. However, some cases of early-onset Stargardt disease show cone and rod dysfunction on ERG, which portends a more aggressive course.^{9,10} Thus, electroretinography would provide correlative information but would not confirm a specific diagnosis. Fundus autofluorescence can show early central retinal atrophic changes with or without radiating flecks,¹⁰ however, there is concern that the extremely bright light used in testing could damage the compromised photoreceptors.¹⁰ OCT shows intraretinal and subretinal flecks arising from degenerated photoreceptor segments leading to hyper-reflective deposits on the apical surface of the retinal pigment epithelium.^{12,13} These deposits disrupt the interdigitation and ellipsoid zones adjacent to the external limiting membrane, leading to thinning of the outer nuclear layer.¹² Fluorescein angiography shows absence of choroidal fluorescence (termed a *dark* or *silent choroid*) in the majority of cases.¹⁴ Mucus membrane biopsy to look for intracellular inclusions, or peripheral blood smear to look for vacuolated lymphocytes were once standard confirmatory tests for Batten disease but have now been superseded by genetic testing. If peripheral blood smear analysis is rapidly available, this could be performed simultaneously with blood draw for genetic testing. Clinical trials and other treatments are in development for both Batten disease and Stargardt disease, so accurate diagnosis is essential (www.clinicaltrials.gov).

This case demonstrates how behavioral changes and overlooking can accompany the devastating central visual loss of Stargardt disease, and how, in the absence of objective neurologic findings, these features need not signify a potentially life-threatening disease.

Patient consent

Written patient consent was obtained from the Mother.

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All authors attest that they meet the current ICMJE criteria for authorship.

Declaration of competing interest

None.

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References

- Spalton DJ, Taylor DSI, Sanders MD. Juvenile Batten's disease: an ophthalmological assessment of 26 patients. *Br J Ophthalmol.* 1980;64:726–732.
- Collins J, Holder GE, Herbert H, Adams GGW. Batten disease: features to facilitate early diagnosis. *Br J Ophthalmol.* 2006;90:1119–1124.
- Shultz A, Kohlschutter A, Mink M, Simonati A, Williams R. NCL diseases: clinical perspectives. *Biochim Biophys Acta.* 2013;1832:1801–1806.
- Wright GA, Georgiou M, Robson AG, et al. Juvenile Batten disease (CLN3): detailed ocular phenotype, novel observations, delayed diagnosis, masquerades, and prospects for therapy. *Ophthalmology.* 2020;4:433–445.
- Borzog S, Ramirez-Montealegre D, Chung M, Pearce DA. Juvenile neuronal ceroid lipofuscinosis (JCNL) and the eye. *Surv Ophthalmol.* 2009;54:463–471.
- Weleber RG. The dystrophic retina in multisystem disorders: the electroretinogram in neuronal ceroid lipofuscinoses. *Eye.* 1998;12:580–590.
- Biswas A, Krishnan P, Ariabadi A, Blaser S, Mercimek-Andrews S, Shroff M. Expanding the neuroimaging phenotype of neuronal ceroid lipofuscinoses. *Am J Neuroradiol.* 2020;41:1930–1936.
- Adams HR, Kwon J, Marshall FJ, de Bleeck EA, Pearce DA, Mink JW. Neuropsychological symptoms of juvenile-onset Batten disease: experiences from 2 studies. *J Child Neurol.* 2007;22L:621–627.
- Rotenstreich Y, Fishman GA, Anderson RJ. Visual acuity loss and clinical observations in a large series of patients with Stargardt disease. *Ophthalmology.* 2003;110:1151–1158.
- Tanna P, Strauss RW, Fujinami K, Michaelides M. Stargardt disease: clinical features, molecular genetics, animal models and therapeutic options. *Br J Ophthalmol.* 2017; 101:25–30.

11. Good WV, Crain LS, Quint RD, et al. Overlooking: a sign of bilateral central scotomata in children. *Dev Med Child Neurol.* 1992;34:61–79.
12. Sparrow JR, Marsiglia M, Allikemets R, et al. Flecks in recessive Stargardt disease: short-wavelength autofluorescence, near-infrared autofluorescence, and optical coherence tomography. *Invest Ophthalmol Vis Sci.* 2015;58, 5029–2039.
13. Heath Jeffery RC, Chen FK. Stargardt disease: multimodal imaging: a review. *Clin Exp Ophthalmol.* 2021;49:498–515.
14. Uliss AE, Moore AT, Bird AC. The dark choroid in posterior retinal dystrophies. *Ophthalmology.* 1987;94:1423–1427.