Early ocular findings in Cohen syndrome: case report and Canadian survey study

Cohen syndrome (CS) is an extremely rare genetic disorder characterized by systemic and ocular findings, with fewer than 1000 cases estimated worldwide. The condition is caused by biallelic mutations in the vacuolar protein sorting 13 homolog B (VPS13B) gene. A diagnosis may be suspected in a child presenting with global developmental delay, hypotonia, microcephaly, slender hands and feet, neutropenia, and dysmorphic facial features (down-slanting palpebral fissures, hypertelorism, short philtrum, prominent upper teeth, maxillary hypoplasia, and micrognathia). Other typical facial characteristics in CS include thick eyebrows, thick bushy hair, low hairline, and long and thick eyelashes. Patients with CS have been described to be sociable with a cheerful disposition. Myopia and retinochoroidal dystrophy are very common, whereas strabismus, ptosis, and lens opacities are occasionally present.

Owing to the rarity, nonspecific presentation, and apparent lack of family history, diagnosis may be delayed until later childhood. As such, reports of early findings in CS are scarce. Here, we describe 6-year longitudinal data from a child with CS beginning at day 1 of life. Motivated by this case, we additionally undertook a short survey study to determine the experience of pediatric ophthalmologists in Canada with this disorder.

A 1-day-old male born by C-section after uncomplicated term pregnancy was referred for ptosis. There was no contributory family history and no consanguinity. Systemic examination was normal. Ophthalmologic examination revealed isolated congenital left-sided ptosis. Anterior and posterior segments were normal. Ptosis was repaired at 2 months.

At 9 months, ptosis repair was stable but the retina demonstrated subacute macular hyperpigmentation. Refractive error was $-4.75+0.50 \times 100^\circ/-4.50+0.50 \times 90^\circ$ (OD/OS). Assessment by general pediatrics at 10 months noted global delay, hypotonia, small mouth, and neutropenia. Magnetic resonance imaging of the head showed no evidence of microcephaly, and screening microarray was normal. At 29 months, cycloplegic refraction was $-4.75+0.50 \times 100^\circ/-4.50+0.50 \times 90^\circ$. Macular hyperpigmentation remained stable. Glasses were prescribed and resulted in improved visual behaviour. Uncorrected visual acuity improved from 20/190 OU to best-corrected visual acuity (BCVA) of 20/94 OU by Teller acuity cards.

Exome sequencing at 3 years identified 2 pathogenic variants of the VPS13B gene (c.1915C>T, c.6732+1G>A). On testing, both parents harboured one variant each, confirming the disease segregation that established the clinical diagnosis of CS. Refractive error was $-8.00+3.25 \times 115^\circ/-7.50+3.00 \times 80^\circ$ and BCVA was 20/63 OU. Fundus photographs demonstrated bull’s eye macular hyperpigmentation with surrounding retinal elevation (Fig. 1a). Numerous rounded chorioretinal atrophic lesions with largely nummular pigmentary changes were present in the periphery (Fig. 1b). Macular optical coherence tomography (OCT) scans demonstrated bilateral large schitic/cystoid changes in outer and inner nuclear layers with disruption of photoreceptor outer and inner segments in the parafoveal region in either eye and in the temporal macula of the left eye (Fig. 1c). Topical dorzolamide was initiated; however, it was abandoned owing to poor tolerance. Electroretinogram demonstrated severe rod-cone dystrophy (Fig. 2).

Subsequent assessments revealed myopic progression to $-10.50+6.50 \times 115^\circ/-10.00+5.00 \times 70^\circ$ at age 6 years. At this examination under anaesthesia, fundus photographs were stable (Fig. 1d, e). Fluorescein angiography showed no leakage at the macula, whereas the peripheral atrophic scars stained prominently (Fig. 1f). BCVA was 20/50 OU.

To our knowledge, this case is the earliest at which serial ophthalmologic assessments in CS have been reported. The earliest ocular findings of CS in this patient were congenital ptosis and macular hyperpigmentation first noted at 9 months, as well as early onset of progressive myopia requiring spectacle correction at age 2 years. Structural retinal changes on OCT, nonleaking cystoid macular edema (CME), and rod-cone dystrophy were detected after formal diagnosis at age 3 years, although may have been present earlier.

A previous case report of a 13-month-old child with CS described low myopia, abnormal foveal pigmentation, retinal cysts, and rod-cone dystrophy. Fluorescein angiography findings were not reported in that case, although nonleaking CME has been described in an 11-year-old with CS.

Biallelic mutations in VPS13B identified in the proband confirmed the molecular basis of CS phenotype. The VPS13B gene mapped to 8q22.2 codes for multiple transcripts, the longest of which (NM_017890.4) is widely expressed in human tissues and thought to play a role in intracellular transport of proteins within Golgi complex. Knocking down VPS13B expression in the retinal pigment epithelium leads to abnormal glycosylation and might explain the retinal dystrophy seen in CS; however, further studies are needed to confirm this hypothesis.
Fig. 1—Multimodal imaging of the left eye at 3 years of age (A–C) and 6 years of age (D–F). At age 3 years, a bullseye maculopathy with surrounding elevation is present. Punched out chorioretinal lesions are present in the periphery (B). On optical coherence tomography, cystoid/schitic changes and disruption of the photoreceptor outer and inner segments are present (C). At age 6 years, macular findings (D) and peripheral lesions (E) remain stable. Late frame fluorescein angiography demonstrates no leakage at the macula, with prominent staining of peripheral lesions (F).

Fig. 2—Electroretinogram (ERG) at 3 years of age, demonstrating severe rod-cone retinal dysfunction. The dark-adapted (DA) dim light scotopic ERG (DA 0.01) is nondetectable. The DA standard (DA 3.0) and bright flash (DA 10.0) responses are severely reduced and appear to be predominantly driven by dark-adapted cones. The light-adapted (LA) single flash and 30 Hz flicker responses are moderately and severely reduced, respectively.
The present case can provide guidance for following patients with CS in the eye clinic. Retinitis pigmentosa is detected commonly in these patients. Routine OCT may inform treatment decisions given that topical carbonic anhydrase inhibitors may improve CME in retinal dystrophies. In addition to OCT, electroretinogram findings can help characterize and explain vision loss, which is critical as these patients may not verbalize visual complaints. Finally, refractive error should be frequently assessed given that progressive myopia is virtually always present.

To further explore the experience with CS among Canadian ophthalmologists, we undertook a survey study. This was approved by the Queen’s University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board. The survey (Appendix) was developed using Qualtrics (Provo, UT) and distributed to members of the Canadian Association of Pediatric Ophthalmology and Strabismus by email listserv (76 members).

Responses were received from 19 pediatric ophthalmologists (response rate, 25%), with a median of 12 years of practice (range, 2–40 years). Respondents were asked to rate how knowledgeable they were of CS. Three (15.8%) rated “not at all,” 5 (26%) “minimally,” 10 (53%) “somewhat,” 1 (5%) “very,” and 0 “extremely.” Only 8 (41%) had seen at least 1 patient with CS over their entire career. The range of number of patients ever seen by each ophthalmologist was 0–4. Only 4 respondents (21%) currently follow a patient with this diagnosis in their practice. Among those, only 1 patient has been assessed by ophthalmology before a diagnosis of CS was known; this is the patient herein reported. While limitations of this study include low response rate, potential recall bias, and patients possibly being double-counted if shared between practices, these do not alter our conclusions.

Pediatric ophthalmologists in Canada have limited exposure to CS in clinical practice and almost exclusively encounter these patients after the diagnosis has been made. Almost half of pediatric ophthalmologists surveyed believed that they were either not at all or only minimally knowledgeable of CS. This underscores the value of reports describing clinical findings of this rare disease, especially early in its natural history. In the context of myopia, pigmentary retinal changes, undefined developmental delay, and dysmorphic features, an ophthalmologist may be among the first providers with opportunity to initiate referral for genetic testing. This, in turn, has large implications for management of vision loss and family expectations.

**Supplementary Materials**

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcjo.2020.07.011.

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**References**


**Footnotes and Disclosure**

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**Exudative retinal detachment secondary to hypertensive crisis related to membranous nephropathy**

Membranous nephropathy is the most common cause of nephrotic syndrome in Caucasian adults, though rare, with an estimated annual worldwide incidence of 1.2 per 100 000 persons. In membranous nephropathy, autoimmune complexes deposit on and thicken the glomerular basement membrane. Of the patients with membranous nephropathy, 12% proceeded to renal failure in a longitudinal study. Patients with end-stage renal disease on dialysis are at significantly increased risk of exudative retinal