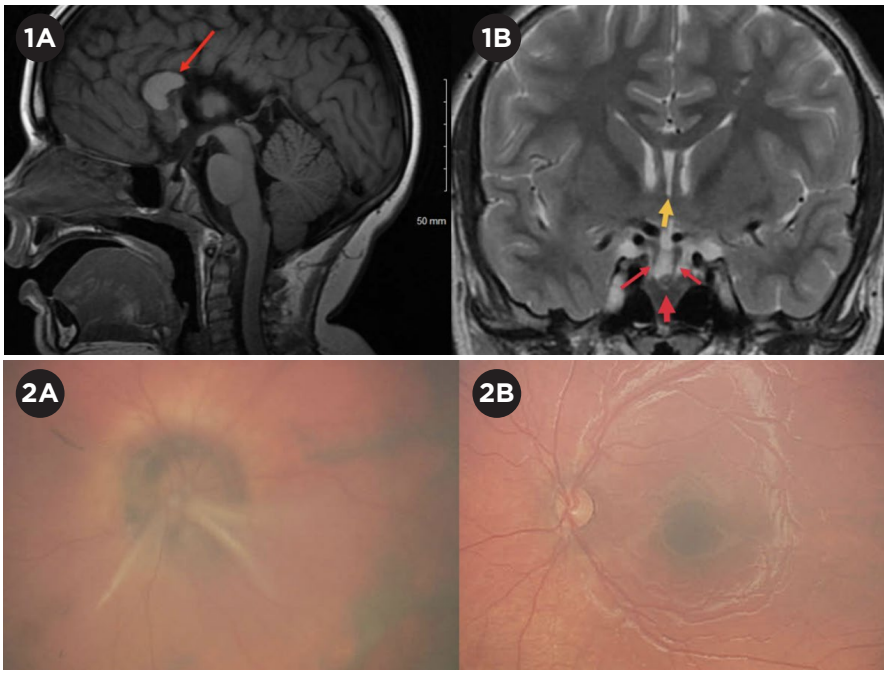
Is It One Anomaly or Two?

Almost 13 years ago, when Samuel Smith* was seen for his six-month well-child checkup, his pediatrician noticed that the infant's right eye was exotropic. Samuel had been born vaginally at 40 weeks' gestational age, and no complications occurred during the pregnancy or birth.

To further investigate the exotropia, magnetic resonance imaging (MRI) of his brain was ordered. This revealed dysgenesis of the corpus callosum, pituitary stalk duplication, and pituitary hypoplasia (Fig. 1). These findings are suggestive of septo-optic dysplasia (SOD).

At this point, Samuel was referred to pediatric ophthalmology for a complete eye examination.



MRI AT SIX MONTHS AND FUNDUS PHOTOS AT AGE 4. *(1) MRI brain findings at six months: (1A) Sagittal MRI using T1 FLAIR sequence shows dysgenesis of the anterior corpus callosum (red arrow). (1B) Coronal T2-weighted MRI shows the cavum septum pellucidum (yellow arrow), duplicated pituitary stalk (thin red arrows), and a hypoplastic pituitary gland (thick red arrow). (2) Fundus appearance at 4 years old: (2A) Fundus photograph of the right eye shows an optic nerve with excavation, hyperpigmentation, blood vessels radially exiting the optic nerve, and a glial tuft. (2B) Left eye shows an unremarkable fundus.*

When Samuel Was 6 Months Old, He Visited Ophthalmology

Samuel's right eye was found to have manifest exotropia and an inability to fix and follow, indicating severely reduced visual acuity. The right eye also had a relative afferent pupillary defect.

No abnormalities were seen in the anterior segment of either eye.

The posterior segment examination of the left eye showed a normal-appearing optic nerve and fundus. However, the posterior segment of the right eye had a large, excavated optic nerve with radial vessels and a peripapillary glial tuft—findings that are consistent with a morning glory optic disc anomaly (MGDA).

Differential Diagnosis

Upon initial evaluation, Samuel appeared to have two separate diagnoses. Based on the midline central nervous system (CNS) dysgenesis and pituitary hypoplasia, the first diagnosis was SOD. However, SOD is classically associated with optic nerve hypoplasia. In contrast, our patient's larger-appearing anomalous optic nerve was more consistent with a MGDA, coloboma, peripapillary staphyloma, or a large optic pit.

BY **VIREN K. GOVINDARAJU, MD, MATTHEW G.J. TRESE, DO, MA, LAUREN FLETCH-MOOREHOUSE, DO, DANIEL FAIN, MD,** AND **MICHAEL T. TRESE, MD**. EDITED BY AHMAD A. AREF, MD, MBA.

At Age 4, Retinal Detachment

Samuel was observed for several years. When he was 4, he developed counting fingers (CF) vision in the right eye. (VA was 20/20 in the left eye.) The left eye still appeared normal, but the right eye—which had previously been anatomically stable—now had a macula-involving retinal detachment. Samuel was taken to the OR for examination under anesthesia, and fundus photography (Fig. 2) was performed to document the appearance of the optic nerves and retinal detachment.

Diagnosis and Management

Based on the clinical appearance of the nerve, including the radial vessels and the peripapillary tuft, the patient was diagnosed with MGDA with associated serous retinal detachment. After extensive discussion, Samuel's parents decided on continued observation of his right eye because of a guarded visual prognosis.

Because Samuel's previous neuroimaging had revealed pituitary abnormalities, he was being followed by a pediatric endocrinologist and a pediatric neurologist. Samuel's growth was below average, and he was found to be deficient in growth hormone. After growth hormone supplementation, he attained normal stature.

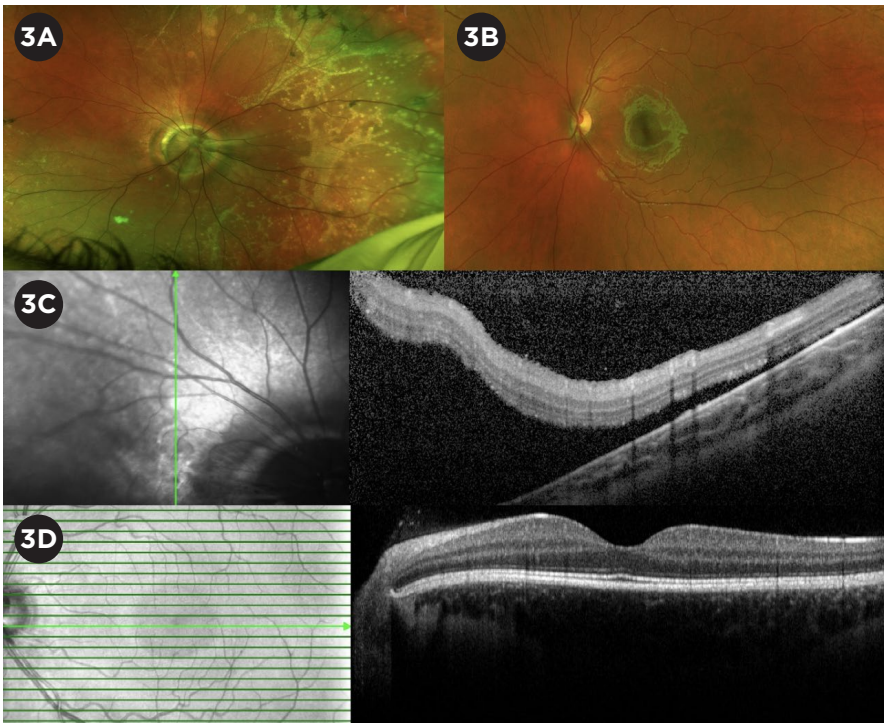
The pediatric neurologist has been performing serial neuroimaging over many years to monitor for the presence of moyamoya disease and chronic cerebrovascular occlusion disease, which may be associated with MGDA. So far, there has been no sign of these diseases.

Our Patient's Course

Samuel is now 13 years old, is of average stature, and is doing well in school. We continue to follow him, and examinations have shown a chronic serous retinal detachment with stable MGDA in the right eye. He has maintained CF vision and normal IOP in the right eye, for nearly a decade after the discovery of his serous retinal detachment (Fig. 3).

Discussion

Although SOD was first described by Reeves in 1941, de Morsier is often credited with its discovery because he reported on 34 patients with an absent septum pellucidum.[1] In addition to these CNS findings, de Morsier noted several ophthalmic associations, including optic nerve dysplasia, bilateral anophthalmia, optic atrophy (both bilateral and unilateral), and optic nerve hypoplasia.[1]



IMAGING AT AGE 13. *(3A) Widefield color fundus photography of the right eye displays an MGDA with atrophic peripheral retinal changes resulting from long-standing serous retinal detachment, and (3B) the left eye is unremarkable. (3C) A vertical peripapillary raster of the right eye taken with spectral-domain OCT demonstrates subretinal fluid emanating from the MGDA consistent with a serous retinal detachment. (3D) SD-OCT of the left eye shows a normal foveal contour.*

It wasn't until almost 20 years later that pituitary dysfunction, most commonly growth hormone deficiency, was described by Hoyt.[2]

Beyond the classic triad—a spectrum of disease. Over the last eight decades, it has become clear that significant phenotypic variability violates the classic teaching that SOD consists of optic nerve hypoplasia, pituitary dysfunction, and midline CNS defects. In fact, Morishima and Arnoff suggested that only 30% of SOD patients display the classic triad.[3] Furthermore, recent research has identified familial cases of SOD and has uncovered genetic associations with mutations in *HESX1* and *SOX2*.[4] Despite these common genetic underpinnings, phenotypic heterogeneity within these families appears to be the norm.[5]

Together, these findings suggest that SOD represents a spectrum of disease that can be referred to as the SOD complex. With this broader definition of SOD, current diagnostic criteria require the presence of only two of the three classic findings.[5]

Our patient's diagnosis of SOD and MGDA. Based on the revised diagnostic criteria that are described above, our patient could be diagnosed with SOD complex by neuroradiologic findings alone.

Despite having classic neurologic and endocrinologic findings of SOD, Samuel did not demonstrate optic nerve hypoplasia. Instead, ophthalmic evaluation revealed an MGDA. This rare anomaly is characterized by an optic nerve that appears excavated, with spokelike retinal vessels and a peripapillary glial tuft; this clinical appearance resembles a morning glory flower.

Generally, VA in eyes with MGDA is poor, largely as the result of an inter-

ruption in the visual system due to the anomalous optic nerve. In addition, long-term VA may be further compromised because of a propensity to develop serous retinal detachments, which occur in roughly one-third of patients with MGDA.[6]

Other cases of midline CNS and optic nerve abnormalities. Some previous reports have provided evidence of midline CNS and optic nerve abnormalities. Loddenkemper and colleagues described a pediatric patient with bilateral MGDA, pituitary stalk duplication, and moyamoya disease.[7] Pierre-Filho and colleagues reported on a pediatric patient with an absent infundibulum and posterior pituitary ectopia with bilateral MGDA.[8]

Potential genetic factors. Although the exact genetic factors that produce the CNS and optic nerve abnormalities are not clearly defined, *PAX6*, *HESX1*, and *SOX2* have been implicated in the pathogenesis of SOD.[1] In addition, *PAX6* mutations have been associated with MGDA formation.[9] Furthermore, within the *PAX6* gene locus, there are multiple regulatory elements that are involved in ocular development, including regulatory elements E180B, HS5, and E60A, which are associated with CNS and optic nerve development.[10] This suggests a possible genetic link that unites these two diagnoses, but further research is required to define the relationship.

Conclusion—for suspected SOD patients, the ophthalmic exam is critical. In conclusion, this case—in which MGDA is present in a patient with SOD—provides an example of the phenotypic heterogeneity of the SOD complex. This association underscores the importance of the ophthalmic examination in patients with suspected SOD.

*Patient name is fictitious.

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Dr. Govindaraju is an ophthalmology resident at the Beaumont Eye Institute in Royal Oak, Mich. **Dr. Fletch-Moorehouse** and **Dr. Fain** are pediatric ophthalmologists at the Helen DeVos Children's Hospital in Grand Rapids, Mich. **Dr. Matthew Trese** was a vitreoretinal surgeon at Associated Retina Consultants in Royal Oak, Mich. *Financial disclosures: None.*

Note: **Dr. Michael Trese,** the 2021 Academy Laureate, passed away on Oct. 21, 2022. This article was submitted prior to his death (aao.org/membership/member-obituaries-detail/michael-trese-md).