

## Small Patient, Big Problems

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**S**truggle and strife may be part and parcel of life, but Cecilia Smith\* seemed to be getting more than her fair share. The Caucasian infant was referred to our pediatric ophthalmology clinic when she was four months old for a complete ophthalmic examination to determine her visual potential after a complicated neonatal hospital course.

### Background

Cecilia was a full-term baby who was born by cesarean section after failure of labor to progress. At birth, she weighed 3,044 g and had normal 1- and 5-minute Apgar scores of 9 and 9. Initially, Cecilia did well and was transferred to the newborn nursery. While there, she became hypothermic with temperatures to 35.6 degrees Celsius and was hypoglycemic with blood sugars as low as 24 mg/dl. She was transferred to the NICU, where the endocrinology team was consulted to evaluate her hypoglycemia. Labs were drawn to evaluate for panhypopituitarism. These revealed low cortisol levels (2.0 µg/dl). All other pituitary hormone levels were normal. Sepsis was also a concern for the cause of her hypoglycemia, but all blood cultures were negative. She was started on hydrocortisone and her blood sugars stabilized, as did her temperature. During her hospital stay, an MRI of her brain was obtained (Fig. 1).

### We Get a Look

When she was seen in our clinic, Cecilia was noted to have roving eye move-

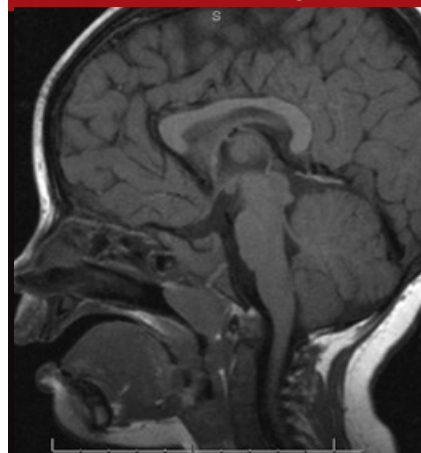
ments, and she was unable to fixate on or follow a target. Pupillary exam was normal, with no evidence of an afferent pupillary defect. Ocular motility exam was grossly normal, but she was noted to have a horizontal, wandering nystagmus. Anterior segment exam was unremarkable. Dilated fundus exam revealed optic nerve hypoplasia in both eyes, but the fundi were otherwise normal. A review of the lab work done in the hospital revealed normal thyroid studies, excluding hypothyroidism as a cause of her optic nerve hypoplasia.

### Our Diagnosis

Based on the clinical evidence of optic nerve hypoplasia and hypopituitarism (low adrenocorticotropic hormone leading to low cortisol) along with MRI evidence of a small pituitary gland, optic nerves and a thin chiasm, a diagnosis of septo-optic dysplasia (de Morsier's syndrome) was made.

Cecilia's parents were counseled on the future likelihood of significant visual impairment. Unfortunately, no therapeutic interventions were available to offer them.

### What's Your Diagnosis?



**SAGITTAL MRI.** We noted thin optic nerves and chiasm, as well as hypoplasia of the pituitary gland.

### A Twist to the Story

Cecilia has been followed in our clinic since her first visit with us at age 4 months. At that initial visit, her only pituitary abnormality was low ACTH. She subsequently developed hypothyroidism, but not in the manner that would be expected for her disease. Her family history revealed that Cecilia's father had an autosomal dominant disorder—multiple endocrine neoplasia (MEN) type 2a—as did several of her cousins. Cecilia was tested and found to be positive for the c-RET proto-oncogene, indicating that she also had the disease. Pediatric surgeons discussed with the family the need for prophylactic thyroidectomy, as the

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risk of medullary thyroid carcinoma is very high in these patients. Thyroidectomy was performed when Cecilia was 3 years old, and she was started on levothyroxine sodium (Synthroid) postoperatively.

Cecilia is now 8 years old and was recently diagnosed with growth hormone deficiency. The pediatric endocrinology team recommended growth hormone supplementation, but Cecilia's parents declined the treatment. Her visual acuity is stable at 20/400 in both eyes, which is consistent with her optic nerve hypoplasia and nystagmus.

### Discussion

**Septo-optic dysplasia (SOD)** is a group of disorders characterized by some combination of: (a) optic nerve hypoplasia, (b) pituitary hypoplasia and (c) absence of the septum pellucidum and/or corpus callosum. It is a rare disorder, with a reported incidence of 1 per 10,000 births.<sup>1</sup>

Patients with SOD may present with ocular abnormalities, such as nystagmus, strabismus or poor visual acuity.<sup>2</sup> Because of pituitary involvement, patients may present with endocrine abnormalities, ranging from a single hormone deficiency to panhypopituitarism. Growth hormone deficiency is the most common endocrinopathy seen in SOD.<sup>1</sup> Patients may also have neurological abnormalities, ranging from epilepsy to mental retardation.<sup>2</sup>

The etiology of SOD remains unclear, although both genetic and environmental causes have been suggested. Recent studies have shown that mutations in the HESX1 homeobox gene may play a role in the pathogenesis of SOD.<sup>1,3</sup> Others have speculated that viral infections or vascular insults during pregnancy may lead to SOD. Because of the heterogeneity of clinical presentations, radiologic findings of SOD are equally widespread. Brain MRI may show hypoplasia of the optic nerves, optic chiasm, septum pellucidum, corpus callosum and/or pituitary gland.

Patients may need regular follow-up with an ophthalmologist, an endocrinologist and a neurologist.<sup>2,4</sup>

**Multiple endocrine neoplasia (MEN)** is a group of disorders characterized by tumors in various endocrine glands. MEN type 1 involves the pancreas, parathyroid and pituitary glands. MEN type 2 is associated with medullary thyroid carcinoma and pheochromocytoma, plus parathyroid tumors in MEN 2a and mucosal neuromas in MEN 2b. These rare disorders have an estimated prevalence of 1 in 20,000 to 40,000 people.<sup>5</sup> They are inherited in an autosomal dominant fashion with high penetrance.<sup>6</sup> MEN 1 is associated with mutations in the MEN 1 gene on chromosome 11, while MEN 2 is related to mutations in the c-RET proto-oncogene on chromosome 10.<sup>7</sup> Management of MEN consists of genetic testing and appropriate tumor screening based on the disease subtype. Again, the approach is interdisciplinary, involving endocrinologists, surgeons and geneticists. Of note, MEN 2 patients often undergo prophylactic thyroidectomy during childhood, since 95 percent of patients with untreated MEN 2 develop medullary thyroid carcinoma over their lifetime.<sup>5</sup>

Currently, there is no literature regarding a connection between SOD and MEN. Patients with either of these disorders will require interdisciplinary management.

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\* Patient name is fictitious.

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