A 4-month old with new onset strabismus

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The case

A full term 4-month old male infant with developmental delay, failure to thrive, and multiple hemangiomas (on scalp, face, abdomen, back, and liver) on propranolol presented to the pediatrician with new onset strabismus (intermittent esotropia) that progressively worsened. Prenatal history was significant for antenatal ultrasound concerning for absent corpus callosum (CC); however, fetal brain MRI was interpreted as normal except for prominence of left ventricle and mild right-sided shift of septum pellucidum (SP). His growth was significant for slow weight gain, thought to be due to reflux. Weight was around 55th percentile at birth, decreased to 1st percentile by about 4 months, and increased to 6th percentile at 5 months old (Figure 1a). Length was <1st percentile and head circumference was preserved (Figure 1b). At the 4 month old well child visit he was found to have developmental delays such as mild head lag, inability to roll over, not passing toy from one hand to the other, not banging two objects together, and not looking when his name was called. He was referred to Early Intervention. Additionally, laboratory studies at this time showed mild degree of central hypothyroidism: low T4 with an inappropriately normal TSH (Dermatology had recommended getting thyroid function tests due to concern for consumptive hypothyroidism in setting of liver hemangiomas) with plans for repeat testing. Overall, he was well appearing without increase in head circumference, without emesis, and with adequate feeding.

He was referred to Neuro-ophthalmology, who noted poor acuities for age and slightly pale/small optic nerves bilaterally. Follow-up brain and pituitary MRI was performed that showed multiple abnormalities including asymmetrically enlarged and dysmorphic left ventricle with thickening of left fornix and diminutive anterior commissure, bilateral optic nerve hypoplasia, thin pituitary stalk, and absent posterior pituitary bright spot (Figure 2a and 2c). Additionally, imaging showed a soft tissue hemangioma over the vertex with possible transcranial vascular communication. He was evaluated by Endocrinology and found to have low morning cortisol, low free T4, low IGF-1, and hypernatremia with low urine osmolality (hypernatremia became even more evident after cortisol and thyroid replacements were started), adequate vitamin D, and normal pre-feed fingerstick blood glucose measurements. A diagnosis of septo-optic dysplasia (SOD) was made based on optic nerve hypoplasia and hypopituitarism.

In terms of the hormonal abnormalities – adrenal insufficiency, central hypothyroidism, diabetes insipidus, and growth hormone deficiency – it is important to highlight the replacement strategy that was initiated. First, hydrocortisone was started based on low 9:45AM cortisol, imaging findings, and need to start levothyroxine (started 3 days after hydrocortisone replacement to avoid precipitation of adrenal crisis). Second, the patient began nighttime subcutaneous desmopressin. Growth hormone (GH) was then initiated based on decreased linear growth, low IGF-1, and clinical context.

Differential Diagnosis

Esotropia is a term used to describe strabismus, or misalignment of the eyes, when there is inward deviation (toward the nose) relative to the fixating eye. It is important to differentiate between strabismus and pseudostrabismus, which occurs when there is false appearance of ocular misalignment due to a wide nasal bridge, epicanthal folds that cover the nasal sclera, or eyelid asymmetry.[1] The corneal light reflex and cover test are two physical exam maneuvers that can be done in the primary care setting to screen for ocular misalignment.[1] According to the American Association for Pediatric Ophthalmology and Strabismus, intermittent esotropia in infants less than 4 months usually resolves on its own and is most likely due to unsteady ocular alignment that is present in newborns during the first few months of life.[2] Conversely, esotropia in infants less than 4 months that is constant or infants greater than 4 months that have any eye crossing should be evaluated by a pediatric ophthalmologist.[2] The causes of strabismus can be categorized into congenital and acquired etiologies. An important cause of acquired strabismus is poor visual acuity that can be due to a variety of conditions such as optic nerve hypoplasia (seen in this patient), amblyopia, cataract, retinoblastoma, and optic nerve tumors.[1] Other causes of acquired strabismus include abnormalities of extra-ocular muscles or their innervation – hydrocephalus, head trauma, encephalitis, intracranial tumors, myasthenia gravis, and cranial nerve III, IV, or VI palsies (which can also be congenital).[1] Additionally, neurodevelopmental disorders and craniofacial syndromes should also be on the differential for both congenital and acquired strabismus.[1]

Diagnosis: Septo-optic dysplasia

SOD is a rare congenital disorder of early brain and eye development. Its prevalence is thought to be approximately 1 in 10,000 children.[3] The exact cause of SOD is unknown in the majority of patients and thought to be a combination of genetic and environmental factors. Genetic abnormalities in genes such as *HESX1*, *SOX2*, and *SOX3* are found in only <1% of patients diagnosed with SOD.[3] SOD is a clinical diagnosis based on having at least two or more features of the classic triad: optic nerve hypoplasia, hypothalamic and/or pituitary abnormalities, and midline brain defects.[3] The diagnostic challenges stem from the spectrum of severity, variable presenting signs/symptoms, and numerous terms for conditions related to SOD (such as de Morsier syndrome, Optic Nerve Hypoplasia (ONH), Multiple Pituitary Hormone Deficiency (MPHD), SOD plus syndrome). Some children present at birth with multiple congenital anomalies while others present as infants or toddlers with failure to thrive or global developmental delay. Webb and Dattani present a structured visualization of the various phenotypes that can present within the SOD spectrum using a triangle with each side representing one element of the classic diagnostic triad mentioned.[3] Each side of the triangle depicts the varying degree of severity within each category. Additional studies have also looked at whether SOD can be diagnosed prenatally when midline brain defects are identified on fetal ultrasound or MRI.[4–6] This case of a 5-month old infant diagnosed with SOD based on bilateral optic nerve hypoplasia and hypopituitarism highlights the importance of astute, multi-dimensional specialty referrals as well as timely diagnosis and treatment.

Follow-up

This patient was seen by Neurology and underwent EEG that was normal. Neurogenetics was consulted who recommended whole exome sequencing given the patient's hemangiomas and

other brain MRI findings did not clearly fit within the clinical spectrum of SOD. The genetic workup was unrevealing. Furthermore, given hemangiomas over scalp, brain abnormalities, and eye involvement, a diagnosis of PHACE syndrome was considered (Posterior fossa brain malformations, Hemangiomas of face, Arterial anomalies, Cardiac anomalies, and Eye abnormalities). However, he was referred to Cardiology and had normal cardiac evaluation.

Discussion

This patient, who initially underwent fetal brain MRI for abnormalities detected on antenatal ultrasound, was eventually diagnosed at 5 months old with SOD and associated developmental delay, optic nerve hypoplasia, and panhypopituitarism. The case presented highlights various questions surrounding a diagnosis of SOD. First, is a prenatal diagnosis of SOD feasible? Infants with pituitary hormone deficiencies, specifically cortisol and thyroid hormone, are at increased risk of detrimental effects on the developing brain and body. Early diagnosis would allow for both timely hormone replacement if abnormalities are identified on laboratory studies and early involvement of services such as physical/occupational therapy. Several studies have examined the association between midline brain defects detected on prenatal imaging (ultrasound/MRI) and a postnatal diagnosis of SOD.[4–6] A retrospective cohort study done by Shinar et al. examined all fetuses that presented with non-visualized septal leaflets (due to absent SP) on ultrasound at Ontario Fetal Centre between January 2008 and June 2019.[4] Of the 214 fetuses with absent septal leaflets, 18 were classified as having prenatally suspected isolated SOD and, of those, 12 mothers opted to continue pregnancy and delivery liveborn infant.[4] Clinical outcomes were available for 10 of the patients, and 5 of whom had findings that fulfilled criteria for SOD (one met all 3 criteria and four met 2 criteria).[4] Thus, the minority of patients found to have SP abnormalities prenatally develop a clinical diagnosis of SOD (5 of 18 patients or 27.7%).

The midline defect these studies focus on is an absent septum pellucidum. Interestingly, in our patient's case, it was a different midline brain defect of concern prenatally – an absent CC. In the study mentioned by Shinar et al., anomaly of CC was not included in the study population because it was considered to be outside of a suspected prenatal diagnosis of SOD.[4] In regards to our patent, the fetal brain MRI did show both CC and SP; however, the SP had right-sided shift with asymmetric ventricles. This was thought to be of unknown significance and no follow-up was recommended. This highlights the heterogenous nature of imaging findings and importance of interpreting imaging results in the context of hormone function and vision assessment, which is nearly impossible when a patient is in utero. Additionally, the newborn screen – a heel stick blood test for various genetic and metabolic abnormalities between 24-48 hours old – for hypothyroidism is not always reliable given TSH can be normal in central hypothyroidism.

Another question brought forth by this clinical case is: what is the spectrum of anomalies that should be included when considering a diagnosis of SOD? This is relevant because there is also the entity known as SOD plus syndrome, which encompasses the diagnostic criteria of SOD in addition to evidence of cortical dysplasia, which might present with more severe neurologic impairment. This example also highlights the practicality of using a framework such as the one Webb and Dattani use that emphasizes the varying degree of severity within each diagnostic criteria within SOD – brain findings, hormonal abnormalities, and eye/vision abnormalities. It is important to note that there is a spectrum of neuroimaging findings that range from no midline brain defects to patients with holoprosencephaly. This patient fulfilled the clinical criteria for a

diagnosis of SOD; however, he did not have the classic neuroimaging findings. Figure 2d demonstrates the classic neuro-imaging findings of SOD compared to the findings seen in this patient. The case presented emphasizes the importance of thinking outside the box when findings don't fit nicely within a diagnosis. Our patient had multiple hemangiomas and concern for transcranial vascular communication which is not seen with SOD, but can be seen with another condition called PHACE syndrome. Thus, neurogenetics recommended referral to cardiology to exclude cardiac anomalies that can be seen with PHACE syndrome.

Diagnostic categories are helpful to offer families thoughtful and evidence supported information about prognosis, and to guide monitoring for hormonal abnormalities. Studies show hormonal abnormalities present earlier with MPHD – a diagnosis along the SOD spectrum with isolated pituitary hormone deficiencies without midline defects or optic nerve hypoplasia – as compared to SOD.[7] Nevertheless, it is difficult to predict if or when hormonal abnormalities will present in patients with SOD. Long-term Endocrinology follow-up is usually recommended. An accurate diagnosis allows physicians to better understand the natural history of disease progression and with which specialties these children need close follow-up. In conclusion, SOD is a phenotypically diverse condition that requires multi-subspeciality involvement. This case emphasizes the challenges associated with prenatal diagnosis; nonetheless, early diagnosis and treatment are necessary to avoid preventable adverse outcomes and to give children the chance to optimize their developmental potential.

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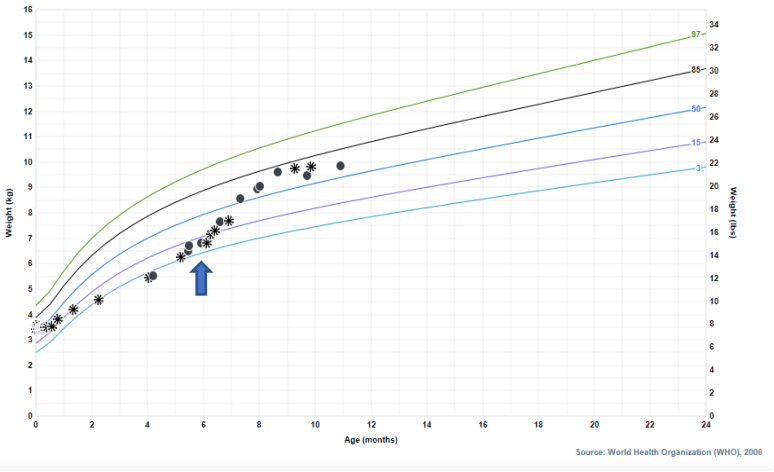

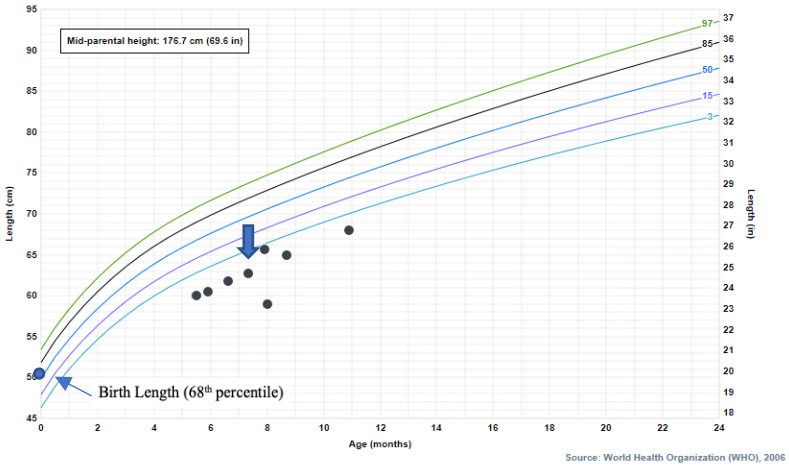

Figure 1: Growth Charts a. WHO weight curve with arrow indicating when hydrocortisone and levothyroxine replacement was initiated b. WHO length curve with arrow indicating when growth hormone replacement was initiated

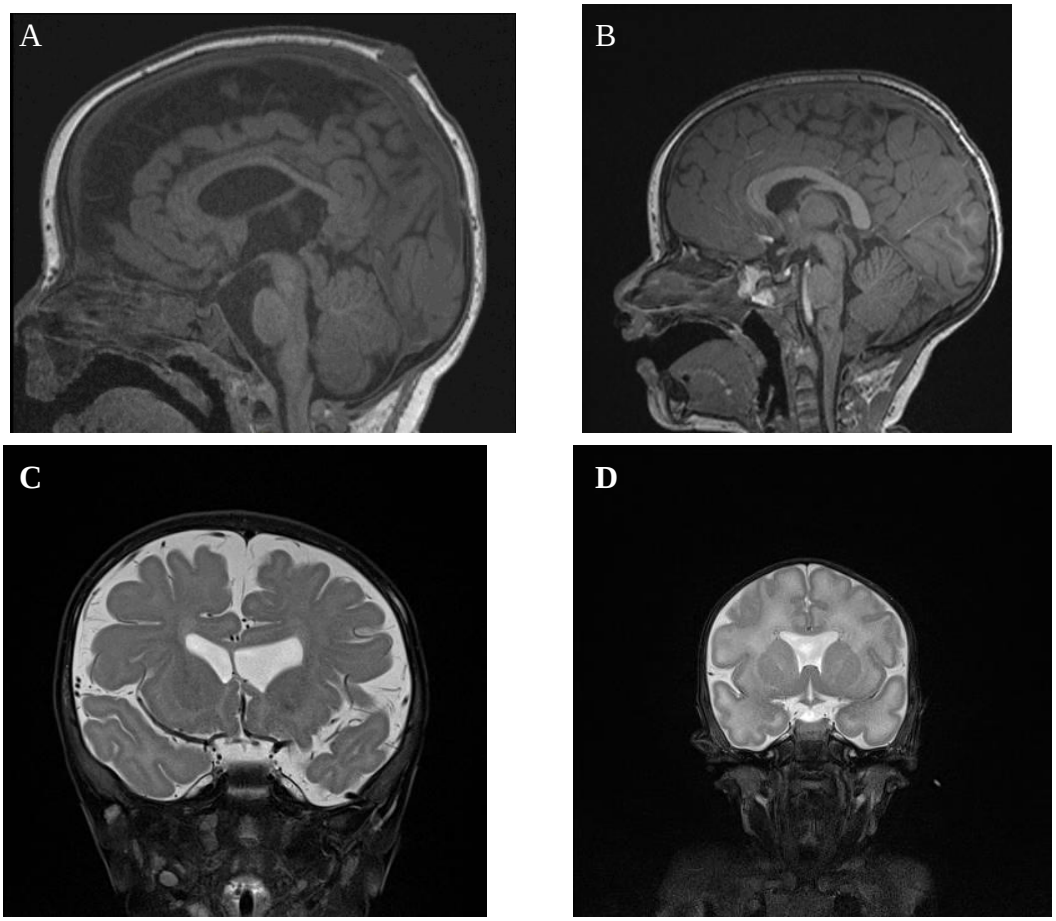

Figure 2: Brain and Pituitary MRI
A. Sagittal view with absent posterior pituitary bright spot and thin pituitary stalk B. Normal sagittal T1 image from another patient with bright signal of pituitary neurohypophysis C. Coronal T2 showing the thin optic chiasm and thin pituitary stalk D. Classic MRI appearance of SOD in another case with absence of the septum pellucidum and box shaped frontal horns in communication