SCIENTIFIC REPORT

Infantile infection and diabetes insipidus in children with optic nerve hypoplasia

S P Donahue, A Lavina, J Najjar

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Background: Bilateral optic nerve hypoplasia (BONH) is often associated with other central nervous system midline abnormalities (septo-optic dysplasia). Hormonal dysfunction, caused by anterior (cortisol) and posterior (ADH) pituitary involvement, can be sudden, severe, and life threatening.
Methods: Case series. Three cases of septo-optic dysplasia (SOD) presenting as infantile infection with associated diabetes insipidus are reported. The diagnosis of SOD was suspected only after ophthalmological evaluation; further evaluation led to the diagnosis of panhypopituitarism.
Conclusions: A high index of suspicion is required to diagnose SOD in children when the disorder presents with infantile infection and hypernatraemia. Early warning signs of neonatal jaundice and hypoglycaemia should prompt ophthalmological evaluation.

Optic nerve hypoplasia (ONH) is a congenital abnormality of the optic nerve characterised by a small optic disc located within a normal scleral canal. It is often associated with midline central nervous system anomalies such as absence of the septum pellucidum or agenesis of the corpus callosum, and is then called septo-optic dysplasia (de Morsier's syndrome). The associated hypothalamic and pituitary dysfunction can produce hypoglycaemia, hypothyroidism, growth retardation, diabetes insipidus, and a lack of glucocorticoid response to stress, which can be life threatening.[1] We recently encountered three infants thought to be normal who presented with infantile infection severe enough to warrant hospitalisation. All developed diabetes insipidus, and were later found to have bilateral ONH. Two had history of neonatal jaundice and neonatal hypoglycaemia. We believe that undiagnosed pituitary and endocrine dysfunction contributed to the severity and morbidity of their infections. The presence of jaundice and hypoglycaemia in the neonatal period should prompt ophthalmological evaluation.

CASE 1

An 11 week old white male was sent to a community hospital by his grandmother after becoming ''limp'' and ''floppy'' and sleeping through his feeds. Gestational history was significant for recurrent maternal genital herpes, and alcohol, cocaine and marijuana abuse until the seventh month of pregnancy. The child weighed 6 lb 7 oz (2.92 kg) at birth. He experienced hypoglycaemia and jaundice in the neonatal nursery, was treated and released, and appeared normal until presentation.

Upon presentation, the child's heart rate was 50 beats/min, and he was lethargic and hypotonic. His serum sodium was 154 mg/dl, and white blood cell (WBC) count was 17 000. Lumbar puncture revealed WBC = 14, red blood cells (RBC) = 295, protein = 156 mg/dl, glucose = 36 mg/dl, and a normal gram stain. The child was given a presumptive diagnosis of viral meningitis (based upon LP results and normal cerebrospinal fluid (CSF) cultures), but was started on cefotaxime (100 mg/kg/day) and aciclovir (30 mg/kg/day). The sodium remained high despite fluid replacement and hypo-osmolar urine output. The child was noted to have unequal pupils, and a non-contrast head computed tomograph (CT) at that institution revealed a hypodense frontal lobe irregularity of unclear aetiology.

The child was then transferred to our institution, where hydration was continued and 1-deamino-8-D-arginine vasopressin (DDAVP) was begun for central diabetes insipidus. Other laboratory abnormalities included anaemia (HCT 26%), hyperbilirubinaemia (3.7 mg/dl), and several transient episodes of marginal hypoglycaemia (glucose in lower 60 seconds). TORCH titres were negative for acute infection. Thyroid hormone and serum cortisol levels were both low: TSH = 14.7 μU/ml, FT4 = 0.5 μU/ml; serum cortisol = 1 μg/dl. Brain magnetic resonance imaging (MRI) revealed an elongated and tubular fourth ventricle, absent septum pellucidum, small corpus callosum, small optic nerves and chiasm, interdigitation of the gyri in the frontal lobes, and atrophic basal ganglia. The normal posterior pituitary bright spot was absent.

Our evaluation found nystagmus with no aversive response to bright light. The right pupil was 4 mm and the left was 3 mm, each with minimal reaction. Funduscopic examination revealed small, pale optic nerves bilaterally. Following control of the endocrine problems, the child's condition stabilised, and he was sent home on DDAVP, hydrocortisone, and Synthroid.

CASE 2

A 5 week old previously healthy girl had a 2 day history of cough, congestion, and fever. Over 24 hours, she became less active and stopped eating. She was admitted to another hospital for a septic examination. Pregnancy was complicated by gestational diabetes but birth was at 35 weeks gestation and she weighed 5 lb 7 oz (2.47 kg). There was no neonatal jaundice or hypoglycaemia. The mother denied using valproate, nalidixic acid, or LSD.

Admission laboratory tests showed a WBC count of 2500 with 9% segmented and 27% banded cells, and a serum sodium of 156 mg/dl with hypotonic urine. Initial lumbar puncture revealed numerous Gram positive cocci with a positive group B streptococcal antigen. Cultures of blood and spinal fluid yielded group B streptococcus. The child was placed on ampicillin and gentamicin. The hospital course was complicated by fluctuating sodium levels, which responded to DDAVP. Serum growth hormone and thyroid hormone were low, but a cortisol stimulation test was normal.

At age 8 months, the patient was evaluated and treated elsewhere for large angle esotropia. Two years later, following

Abbreviations: ACTH, adrenocorticotrophic hormone; BONH, bilateral optic nerve hypoplasia; SOD, septo-optic dysplasia

two strabismus surgeries, the child was referred for ophthalmological examination because of nystagmus and persistent esotropia. Visual acuity was uncentral, unsteady, and unmaintained in both eyes. She had nystagmus and approximately 35 prism dioptres of esotropia. Both optic nerves were small and hypoplastic. The previous ophthalmology notes did not mention abnormal optic nerves, and did not indicate a examination for the nystagmus. Outpatient head MRI revealed encephalomalacia, schizencephaly in the right hemisphere, and an absent posterior pituitary bright spot. A diagnosis of septo-optic dysplasia was made at this time. She was treated with replacement therapy for deficiencies of growth hormone, thyroid hormone, and ADH.

CASE 3

A 3½ month old white male presented to an outside hospital with 3 days of cough, congestion, poor oral intake, increased work of breathing, and a fever of 102.4°F. He was born at 39 weeks gestation to a nulliparous mother. The pregnancy was complicated by severe maternal dehydration secondary to food poisoning and viral gastroenteritis at 6.5 months and 7.5 months gestation respectively. The mother had been treated with antibiotics before delivery for positive cultures of group b streptococcus. Jaundice and hypoglycaemia occurred in the newborn nursery.

Before transfer to our institution, he had been treated for respiratory syncytial virus (RSV) bronchiolitis, and otitis media, and had a serum sodium of 155 mg/dl.

On admission at our institution, temperature was 100.7°F, respirations 48/min, and pulse 177/min. Pus was visible behind the right tympanic membrane. Nystagmus, unequal pupils, and an exotropia were noted by the admitting service. Sodium reached 162 mg/dl despite intravenous fluid replacement.

Our examination demonstrated right hemiparesis, right amaurotic pupil, right gaze palsy, left relative afferent pupillary defect, left gaze paretic nystagmus, left ptosis, and an anisocoria consistent with left Horner's syndrome. Dilated fundus examination demonstrated bilateral optic nerve hypoplasia. Given these findings and the persistent hypernatraemia, we suspected septo-optic dysplasia with panhypopituitarism, and recommended urgent paediatric endocrinology consult and neuro-imaging.

MRI showed hypoplastic optic nerves and optic tracts, absent septum pellucidum, bilateral schizencephaly, bilateral cortical dysplasia, an attenuated small hypothalamic stalk, and anterior corpus callosum, and absent pituitary bright spot. The brainstem was remarkably normal. Paediatric endocrinology evaluation confirmed central diabetes insipidus, hypothyroidism, and low serum cortisol (6.6 µg/dl). The patient's status eventually improved and he was discharged.

DISCUSSION

We report three infants with previously undiagnosed bilateral ONH who presented with infantile infection and hypernatraemia. Two had neonatal jaundice and hypoglycaemia, which is often a harbinger of bilateral ONH and endocrine anomalies. One patient (case 2) had an intact septum pellucidum, but other abnormalities typically seen with BONH and SOD. In all three cases, the parents had noticed an ocular abnormality in early life. Neuro-imaging found significant midline CNS abnormalities in all three, including absence of the normal posterior pituitary bright spot. In one case, the pituitary images were read as normal until they were reviewed by us. All three children had SOD diagnosed only after our ophthalmological evaluation.

The relation between bilateral ONH and mid-line CNS abnormalities has been well documented.[2–7] These midline defects are believed to be caused by an insult during prosencephalic development (gestation week 13) which affects midline structures including the cerebral hemispheres, the hypothalamus, and the pituitary, and produces pituitary and hypothalamic abnormalities.[8–11] Ectopia or absence of the posterior pituitary bright spot is a very sensitive MRI indicator of anterior pituitary dysfunction,[5 12] and occurred in all three patients. This sign is also a marker for diabetes insipidus in patients with BONH.

In addition to diabetes insipidus, other associated endocrine abnormalities in BONH include adrenocorticotrophic hormone (ACTH) deficiency,[1 2] thyroid stimulating hormone deficiency, and growth hormone deficiency.[4] Cortisol insufficiency often becomes manifest only during periods of stress. Brodsky *et al* recently reported five children with bilateral ONH who experienced sudden death during stress, and postulated this to be due to an abnormal cortisol response.[1] We believe our patients began with mild childhood infectious symptoms that progressed to meningitis because of insufficient endocrine responses to the stress of the infection. Two of our patients had abnormal cortisol response during physiological testing. Low cortisol levels lead to poor counter-regulatory systems causing hypoglycaemia and/or low blood pressure. This, in addition to diabetes insipidus with resultant dehydration and hypernatraemia, can cause significant morbidity. Therefore, it is important that evaluation of the hypothalamic-pituitary-adrenal axis be performed as part of the endocrine examination for patients diagnosed with BONH, or those having unilateral ONH but neonatal jaundice or hypoglycaemia.

Our cases illustrate how the endocrinological abnormalities seen with OHN can complicate a child's normal response to typical childhood illnesses. SOD should be in the differential diagnosis of any infant with hypotonia, lethargy, or jaundice, who has unexplained hypoglycaemia or hypernatraemia, especially if ocular findings such as nystagmus or poor visual behaviour are present. Prompt ophthalmological and endocrine consultation and MRI imaging are mandatory for establishing the extent of hypothalamic-pituitary axis abnormalities, and minimising morbidity.

Authors' affiliations

S P Donahue, A Lavina, Department of Ophthalmology and Visual Sciences, Vanderbilt University School of Medicine, Nashville, TN, USA
S P Donahue, Department of Neurology, Vanderbilt University School of Medicine, Nashville, TN, USA
J Najjar, S P Donahue, Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN, USA

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Correspondence to: Sean P Donahue, MD, PhD, Department of Ophthalmology and Visual Sciences, Vanderbilt University School of Medicine, 8000 Medical Center East, Nashville, TN 37232-8808, USA; sean.donahue@vanderbilt.edu

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