Septo-Optic Dysplasia

Optic Nerve Hypoplasia

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Septo-Optic Dysplasia (SOD)

Congenital malformation syndrome
- Underdevelopment of the optic nerve
- Pituitary dysfunction
- Abnormal formation of structures along the midline of the brain

Optic Nerve Hypoplasia Syndrome (ONH)
- Thought to be more accurate term
- SOD and ONH terms overlap

ONH/SOD

- Reported incidence of 1 in 10,000 newborns
- Prevalence of ONH in Sweden quadrupled between 1980 and 1999 to 7.1 per 100,000
- In 2006, a report from England described the prevalence of ONH as 10.9 per 100,000 children
- Equal prevalence in males and females
- First described in 1941
- Also known as De Morsier Syndrome
Optic Nerve Hypoplasia

- Has become a leading cause of congenital blindness
- In 1997, bilateral ONH surpassed retinopathy of prematurity as the single leading cause of infant blindness in Sweden
- Can present with nystagmus
- Smaller than usual optic disc
- Vision varies from normal to completely blind
- Bilateral or Unilateral involvement
- Non-progressive

Abnormal Formation of Midline Brain

- Corpus callosum
  - Band of tissue that connects the two hemispheres
- Septum pellucidum
  - Separates the ventricles
Optic Nerve Hypoplasia

1. Definition: underdeveloped optic nerve in one or both eyes
2. Defect estimated to occur between 7th and 15th week of gestation
3. Double ring sign, optic nerve is surrounded by a yellow peripapillary ring of sclera
4. Visual acuity not directly correlated to exam findings
Optic Nerve Development

- 7th week: axons extend down optic stalk
- 11th week: axons reach lateral geniculate nucleus (LGN)
- 16th week: 3.5 million axons in nerve
- 40th week: 1.2 million axons in nerve

Pathogenesis of ONH

- Nerve fibers fail to reach target destination and/or
- Fibers undergo excessive apoptosis

www.focusfamilies.org
Double ring sign in ONH

Borchert M, 2013
Visual Possibilities in ONH

- Vision described as constant blurriness
- Poor peripheral vision
- Poor depth perception
- Mild photophobia
- 80% of bilateral cases are legally blind
- Most children experience some improvement in their vision in the first few years of life.
  - May be due to improvement in superimposed cortical vision impairment, or due to optic nerve myelination that occurs in the first 4 years of life leading to improved axonal conduction

Pituitary Dysfunction in ONH

- Onset and range of hormonal dysfunction varies considerably
- Ranges from normal function to complete deficiency of posterior and anterior pituitary
- Presentation can include newborn hypoglycemia, prolonged jaundice and microopenis
- Hormonal function not static

Hypopituitarism

Deficiencies in:
- Growth hormone (GH)
- Thyroid hormone (TSH)
- Cortisol (ACTH)
- Vasopressin (ADH)
- Sex hormones (FSH/LH)
Prevalence of endocrinopathies in young children with optic nerve hypoplasia (ONH).

- Prospective observational study, Geffner et al. 2006
- N = 47, mean ± SD 15.2 ± 10.6 months) were followed until 59.0 ± 6.2 months of age
- Prevalence of endocrinopathies was 71.7%
- Endocrinopathies were not associated with ONH laterality, absence of the septum pellucidum, or pituitary abnormalities on neuroimaging

Frequency (%) of Hormonal Deficiency in ONH

- Growth Hormone Deficiency
- Hypothyroidism
- Adrenal Insufficiency
- Diabetes Insipidus

Hypopituitarism in ONH

- Charts of 56 patients with ONH referred between 1990 and 2000 were reviewed by Haddad et al.
- Forty-six patients (82%) had hypopituitarism, with growth hormone deficiency being the most common endocrinopathy
- Evolving pituitary hormone deficiency was observed in two of 37 patients diagnosed with hypopituitarism in the first 3 years of life
Thyroid hormone is crucial for brain development during the first few months to years of life. It influences neuronal migration, axonal outgrowth, and myelination within the central nervous system. To help reduce mental retardation, all states in the US have mandated newborn screening (NBS) programs for congenital primary hypothyroidism.

In 18 states, including California, NBS involves initial measurement of thyroid-stimulating hormone (TSH), elevations of which prompt confirmatory evaluation of thyroid function. Low TSH levels are not reported. Central hypothyroidism not identified with TSH-based NBS methods.

In 1992 Children’s Hospital Los Angeles established an ONH registry to collect ophthalmological, endocrinological, and neuropsychological data from subjects with a diagnosis of ONH in at least one eye. As of November 2007, this registry had clinical data for 214 subjects diagnosed with ONH at <36 months of age by a single neuro-ophthalmologist. Children in the registry are followed annually through 5 years of age.
**Thyroid Newborn Screen in ONH**

Fink, C 2012

New York State Method of Screening (First Tier): Screening for congenital hypothyroidism is accomplished by measuring total T4 levels in dried blood spot specimens by immunoassay.

Second Tier Screening: If the T4 value is below the daily cut-off level, TSH testing is done.

Ma et al in 2010 reported 8/214 children who developed central hypothyroidism at 20-51 months:
- Previous levels normal
- All had hyperprolactinemia
- 5/8 already had GH deficiency

**NYS Newborn Screening**

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**Evolving Central Hypothyroidism in ONH**

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Prolactin Regulation

Prolactin elevation in ONH

- 48.5% hyperprolactinemia seen in Ahmad, et al 2006 cohort (23/47)
- Early hyperprolactinemia (<36 months) correlates with the presence of hypopituitarism, (OR 2.58; 95% CI 1.16, 5.73), specifically with growth hormone deficiency (OR 2.77; 95% CI 1.21, 6.34) in children with ONH, Vedin et al, 2002

Clinical Management of ONH, Recommendations of Mark Borchert, MD

- Ophthalmoscopic exam is warranted in all neonates with jaundice and recurrent hypoglycemia, especially if associated with temperature instability
- All infants with poor visual behavior, strabismus, or nystagmus by 3 months of age should have an ophthalmoscopic examination to rule out ONH
Vision Management of ONH

- Vision status should be monitored at least annually, and any refractive errors should be treated when the visual acuity reaches a functional level.
- Children with unilateral or markedly asymmetric ONH should not be treated with patching. Although vision can improve in the worse eye of asymmetric ONH with patching, it rarely improves enough to be useful to the patient, and requires prolonged patching to maintain. This can be detrimental to the overall development of these children.
- Surgical correction of strabismus should be reserved for patients with symmetrical functional vision in both eyes. Surgery should be postponed until the strabismus is an impending psychosocial issue.

American Association for Pediatric Ophthalmology and Strabismus (AAPOS)

- Some patients with nystagmus will acquire a head turn or tilt if the nystagmus slows down with a certain head position.
- The head position where the nystagmus is slowest, or even stopped, is called the null point.
- Decreased nystagmus allows for better vision, and thus the head postures should not be discouraged in these children.

Imaging in ONH

- MRI of Brain
  - Necessary to rule out treatable conditions such as hydrocephalus
  - Findings of schizencephaly or polymicrogyria should prompt neurologic examination for risk of focal deficits or seizures
Endocrine Screening in ONH

- Pituitary screen
  - Fasting morning cortisol and glucose, TSH, free T4, and the growth hormone surrogates: insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3)
  - Less than 6 months of age, labs should include luteinizing hormone, follicle-stimulating hormone, and/or testosterone levels to assess risk of delayed sexual development
  - Monitor growth every 6 months
  - GH stim test if slow growth
  - Free T4 should be reassessed at least semi-annually until two years of age and annually thereafter until at least four years of age

Maternal Factors in ONH

- Reports consistently describe young maternal age and primiparity
- High prevalence of prenatal maternal weight loss or poor weight gain
  - Suggests a potential role for prenatal weight and nutrition in the occurrence of ONH
  - Supported by a report on the geographic clustering of cases of ONH with population factors of deprivation

Maternal Factors on ONH

- ONH has long been linked to recreational (e.g., LSD) or prescription (e.g., anticonvulsants, quinine, antidepressants) drugs
  - Primarily from isolated exposures or case reports
- Population-based case-control study of severe bilateral cases in Sweden
  - Data were obtained from interviews within the first trimester of pregnancy
  - N=156 out of registry of 2 million
  - Increased risk with young maternal age, primiparity, and early prenatal smoking exposure, but not with drug or alcohol exposure.
Maternal Factors in ONH

• Garcia-Filion P, et al in 2010
• Goal to describe and clarify the birth and prenatal characteristics of a large cohort of children with optic nerve hypoplasia
• Descriptive report of 204 ONH patients aged ≤ 36 months, maternal interviews
  • 51% male
  • 85% bilateral, 15% unilateral
  • 76% first child (compared to 40% registry)
  • No evidence of heritability; family history was negative for ONH and there were no siblings affected by ONH
  • Increased frequency of caesarean delivery and fetal distress
  • Predominance of young maternal age and primaparity among cases of ONH
  • 18% (versus 33%) of mothers had smoked at any time during pregnancy was lower (p = 0.001), no other exposures identified.

Maternal Age in SOD

• Murray et al in 2005 retrospectively looked at 30 patients with SOD attending the Royal Hospital for Sick Children, Glasgow. Birth data for the Scottish population were used for comparison.
• Median maternal age in SOD was 21 (range 16-41) years, median maternal age for Scotland of 27.12 (range 25.8-28.6) years. (95% CI 4.8-8.0 years)
• SOD did not differ in birth weight or gestational age at birth.

Genes Implicated in SOD

• HESX1, SOX2, SOX3, and OTX2 are essential for the formation of the eyes, the pituitary gland, and structures at the front of the brain (the forebrain) such as the optic nerves.
• Genetic mutations in cases of ONH are rare, and a specific genotype/phenotype linkage has yet to be found to explain the majority of cases.
• Most cases of SOD are sporadic.
• Familial occurrences (often autosomal recessive) have been rarely described.
• Whole Exome Sequencing (WES)
• Laura Li, PhD at CHLA, Dr. Borchert is performing WES on children with ONH and their first degree relatives.
• Lack of definitive genetic associations has led to a search for prenatal environmental or biological contributors.
HESX1 mutations are an uncommon cause of septooptic dysplasia and hypopituitarism

- Nonfamilial patients (724) with either SOD (n = 314) or isolated pituitary dysfunction, optic nerve hypoplasia, or midline neurological abnormalities (n = 410) screened heteroduplex detection for mutations in the coding and regulatory regions of HESX1
- Overall incidence of coding region mutations within the cohort was less than 1%

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HESX1 mutations are an uncommon cause of septooptic dysplasia and hypopituitarism

Developmental outcomes of children with ONH

- Garcia-Filion et al, 2008
- Prospective analysis of 73 subjects diagnosed with optic nerve hypoplasia at ≤36 months of age for developmental outcomes at 5 years of age
- Neuroradiographic imaging, endocrinologic testing and examination, and ophthalmologic examination: developmental outcomes were assessed by using the Battelle Developmental Inventory:
  - BDI consists of parental interview and individual assessment and includes five domains: personal, social, adaptive, motor, communication and cognitive ability.

Developmental outcomes of children with ONH

- At 5 years of age, developmental delay in 71%.
  - Unilateral, 39% developmental delay.
  - Bilateral optic nerve hypoplasia, 78% developmental delay.
- Corpus callosum hypoplasia and hypothyroidism were significantly associated with poor outcome in all of the developmental domains and an increased risk of delay.
- Absence of the septum pellucidum was not associated with adverse development.
- Six subjects had neither a neuroradiographic nor an endocrinologic abnormality, and of those 4 were developmentally delayed.
Developmental Outcomes in ONH Patients

- Parr et al. in 2010 reported that, in a sample of 83 children with ONH and moderate to severe vision impairment, 37% (31/83) displayed social, communicative and repetitive or restricted behavioral difficulties and the majority of those had a clinical diagnosis of autism spectrum disorder (ASD)
- Children with ONH and/or SOD and visual impairment have a similar risk of developing clinical ASD as other visual impairment groups
  - ASD as high as ¼ for visually impaired
  - Rice in 2009 estimated ASD 1/110 of general population

ASD Features in Blind Children

- Echolalia
- Pronoun reversal
  - children refer to themselves as "he," "she," or "you," or by their own proper name
- Stereotypical motor movements
- Delays in Developing Pretend Play
- Some debate about ASD dx as these are sometimes considered "blindisms"

Sleep Disturbance in ONH

- Rivkees et al. in 2010 studied 19 children with ONH
  - used actigraphy (non-invasive method for continuously measuring activity)
  - 13/19 (68%) had normal sleep
  - 6/19 (32%) with abnormal rhythmicity
  - 100% children with abnormal rhythmicity were had severe visual impairment
  - 85% of children with normal sleep had normal pupillary response in at least one eye vs 17% in poor sleep (1/6)
- Children with disturbed sleep cycles can be treated with
  - Melatonin receptor agonist
  - Non-24, Vanda Pharmaceuticals
    - Tasimelteon™ (HETLIOZ™) became the first approved treatment for Non-24-Hour Sleep-Wake Disorder by the United States (U.S.) Food and Drug Administration on January 31, 2014.
First manifestation is often a visual impairment secondary to ONH
Phenotype is highly variable
Nystagmus usually develops at 1 to 3 months of age followed by strabismus, typically esotropia.
Approximately 80% of children with ONH are bilaterally affected with two-thirds asymmetrically affected
Patients with unilateral ONH, usually diagnosed at a later age than bilateral cases, present primarily with strabismus rather than nystagmus

Presentation of SOD

ONH- Case #1

Presented to Endocrine for evaluation at 4 months old
Family had noted abnormal eye movements and prompted pediatrician evaluation and referral to ophthalmologist
MRI brain confirming bilateral optic nerve hypoplasia
Left optic nerve smaller than right
Small optic chiasm
Absent septum pellucidum
Lateral ventricles dysmorphic: Right schizencephaly
Corpus Callosum intact but thinned
Normal appearance of pituitary, normal bright spot

ONH- Case #1

Uncomplicated pregnancy to 27 year old G1P0 mother, ½ ppd smoking exposure prior to pregnancy known
Uncomplicated vaginal delivery, 7lbs, 20 inches
No neonatal problems, regular nursery
PE: nystagmus, hypotelorism, normal phallus
Labs at 4 months: normal TSH, free T4, Na, BG, and cortisol 12 ug/dl (3.7-19.4)
ONH-Case #1

- Growth excellent
- At 1.5 years low cortisol on AM screen of 4.7 ug/dl, prompted low dose ACTH stimulation testing with peak 8.4 ug/dl
- Other pituitary screens remain intact including reassuring ACTH and cortisol levels
- Severe visual impairment, right worse than left, glasses started at 6 years, Left hemiparesis
- OT, PT, normal education classroom
- Rocking, clapping, loves music

ONH-Case #2

- Presented to Endocrine for evaluation at 4 months old
- Family has noted abnormal eye movements
- Prompted ophthalmology evaluation
- MRI Brain
  - Near complete hypoplasia of both optic nerves
  - Neuroglial cyst
  - Septum Pellicidum present
  - Anterior Pituitary unremarkable

ONH-Case#2

- Uncomplicated full-term pregnancy to 21 year old G1P0, no known exposures
- C/s delivery, 7 lbs, 18 inches
- One week NICU stay for hypoglycemia, IVF weaned
- PE at 4 months, nystagmus
- Labs: normal TSH, free T4 and IGF-1, prolactin 37 ng/ml (0.5-30), low cortisol 2.1 mcg/dl, prompted low dose ACTH stimulation testing with peak of 7.2 mg/dl
ONH-Case #2

- Stress coverage of hydrocortisone
  - Has presentation of adrenal crisis with illness
- Thyroid replacement start by 3 years for downward trend of free T4 (was still in normal range at start)
- Growth consistent at 5%tile without deceleration in tall family at 4 years
  - IGF-1 level not trending up as expected despite good weight gain
  - Offered GH Rx start
- No vision, loves music, no autistic features

ONH-Case #3

- Endocrine consult at 9 days old for persistent hypoglycemia, poor feeder
  - Full term, 7lbs, normal female exam, poor feeder, mother 17 yo G2P0, +THC
- MRI Brain
  - Right optic nerve hypoplasia
  - Ectopic pituitary
  - Normal corpus callosum

ONH-Case #3

- Low cortisol at time of hypoglycemia
- Maintenance hydrocortisone started with resolution of hypoglycemia by 2 weeks
- Thyroid replacement start at 5 weeks for downward trend of free T4
- GH Rx started at 18 months old for growth failure despite good weight gain
- Vision 100% intact unilaterally, esotropia, normal development without autistic features
Stem Cell Treatment for ONH

No viable treatment options available to improve vision
No open NIH trials for ONH/SOD
Families with children affected by ONH are travelling to China seeking stem cell therapy, despite lack of approval in the United States and Europe.
Pediatric neuro-ophthalmologist Mark Borchert, MD, agreed to conduct an independent study when asked by Beike Biotech, a company based in Shenzhen, China, that offers treatment for ONH using donor umbilical cord stem cells injected into the cerebral spinal fluid.

Stem Cell Therapy for Pediatric Optic Nerve Hypoplasia

Treatments consisted of six infusions over a 16-day period of umbilical cord-derived mesenchymal stem cells and daily infusions of growth factors.
Visual acuity, optic nerve size, and sensitivity to light were to be evaluated one month before stem cell therapy and three and nine months after treatment.
No therapeutic effect was found in the two case-control pairs that were enrolled.

Evaluating Effect of Stem Cell Transplantation on ONH

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ONH/SOD Summary

- Associated with young maternal age and primiparity
- No clear genetic cause identified in majority
- About ¾ legally blind, ¾ with brain abnormalities and ¾ with pituitary deficiency
- Prolactin may help predict other pituitary abnormalities
- Early treatment of mild central hypothyroidism should be strongly considered
- China stem cell infusions generally not helpful

References


References