DIFFERENCES AND SIMILARITIES BETWEEN IDIOPATHIC INTRACRANIAL HYPERTENSION, OCULAR MYASTHENIA GRAVIS, OPTIC NEURITIS, AND HORNER’S IN CHILDREN VS. ADULTS

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LEARNING OBJECTIVE
Understand the differences and similarities between children and adults with common neuro-ophthalmic problems

CME QUESTIONS: TRUE/FALSE
1. Like adults, children with IIH tend to be obese and female.
2. White matter lesions on MRI at presentation are predictive of conversion to MS in children with optic neuritis.
3. Carotid dissection is a primary consideration in children with Horner’s syndrome.

KEYWORDS
1. Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)
2. Pediatric Optic Neuritis
3. Ocular Myasthenia Gravis
4. Horner’s Syndrome

INTRODUCTION
Pediatric neuro-ophthalmology is more than just neuro-ophthalmology of little people. Compared with neuro-ophthalmology in adults, in the pediatric subspecialty the diseases are different, with greater emphases on congenital malformations and genetic disorders and less on vascular problems. The approach also varies, particularly with regard to examination techniques and interaction with the parents. In many instances, it is still unclear from a physiologic standpoint why such striking differences exist between disease profiles in adults and children.

The purpose of this talk is to highlight the similarities and differences between adults and children with four common neuro-ophthalmic problems.

IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH)

Similarities between children and adults with IIH.
- Diagnosis is made similarly (papilledema, normal imaging, elevated opening pressure on lumbar puncture)
- Morbidity (vision loss)
- Treatment algorithms (acetazolamide, weight loss, optic nerve sheath fenestration/shunting when vision loss is severe or progressive despite maximal medical therapy) (Rangwala and Liu, 2007).
- Postpubertal patients tend to be female and overweight (Balcer et al. 1999).

Differences between children and adults with IIH.
- In prepubescent children, more thin children, boys, and asymptomatic presentations. Fewer with headaches as well. (Balcer et al. 1999; Rangwala and Liu, 2007)
- More sixth nerve palsies
- Young age makes following with computerized visual field testing difficult
- More cases associated with medication use (tetracycline derivatives, synthetic growth hormone, for instance) (Ko and Liu, 2010)
- MRI-v recommended in addition to MRI in all cases for diagnosis (Rangwala and Liu, 2007)
- Definition of elevated opening pressure varies (280 mm H2O vs. 250 mm H2O) (Avery et al. 2010)
- Better visual prognosis (Soiberman et al. 2011)

OCULAR MYASTHENIA GRAVIS (OMG)

Similarities between children and adults with OMG.
- Juvenile and adult myasthenia gravis are both autoimmune disorders
- Presentation with ptosis, strabismus, and/or ophthalmoplegia (Kim et al. 2003)
- Diagnosis with acetylcholine receptor antibody testing
- Use of ice test or rest test
- Treatment options include pyridostigmine, prednisone, immunosuppression, and thymectomy.

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Differences between children and adults with OMG.

- Other forms to consider in infancy: neonatal myasthenia gravis
- Use of the edrophonium test, repetitive stimulation, or single fiber EMG may not be possible in some children because of lack of cooperation.
- Therefore when the acetylcholine receptor antibody testing is normal, the diagnosis of ocular myasthenia gravis in a child may lack confirmatory testing.
- Amblyopia due to ptosis (deprivational) and ocular misalignment (strabismic) make aggressive treatment more of a priority (Ortiz and Borchart 2008; Pineles et al. 2010)
- Thymectomy in younger children can be performed transthorascopically rather than transcervically or trans-ternally.
- Thymoma rare
- In our series (Pineles et al. 2010), the development of generalized symptoms (23%) was lower than earlier case series of pediatric OMG (36-43%) (Mullaney et al. 2003; McCreery et al. 2002), and that of adult OMG (31-49%) (Bever et al. 1983; Sommer et al. 1997). These rates corroborate the notion that development of generalized symptoms may be less common in pediatric OMG than in the adult population.

OPTIC NEURITIS (ON)

Similarities between children and adults with optic neuritis.

- Clinically, optic neuritis in the pediatric age group is diagnosed by the same criteria used in adults, including sudden or subacute visual loss, central or cecocentral visual field defect, impairment of color vision, afferent pupillary defect, and ocular pain on eye movements.
- Often the initial manifestation of multiple sclerosis (MS).
- According to the ONT, after acute unilateral optic neuritis, adults have a 50% chance of developing MS within 15 years (Optic Neuritis Study Group 2008). Children with optic neuritis are also at risk for development of MS (29%, meta-analysis) (Waldman et al., in press).
- White matter lesions on MRI are predictive of conversion to MS. As established by the Optic Neuritis Treatment Trial, an abnormal baseline brain MRI with white matter lesions is a strong predictor of MS after isolated optic neuritis in adults. Fifteen years after a bout of optic neuritis, 72% of adults with one or more brain MRI lesions at presentation developed MS, in contrast with a 25% conversion rate in those with no lesions (Optic Neuritis Study Group 2008). In children, an abnormal MRI at presentation is likely also predictive. In our study (Bonhomme et al. 2009) 18 patients were followed for more than 24 months, and 3 of the 18 (17%) developed MS. All three patients had an abnormal brain MRI scan at their initial presentation of optic neuritis. None of the patients with a normal brain MRI scan at presentation developed MS over an average follow-up of 88.5 months. Patients with one or more white matter lesions on MRI were more likely to develop MS (3/7 vs. 0/11, p=0.04, Fisher’s exact test). We concluded that children with brain MRI abnormalities at the time of the diagnosis of optic neuritis have an increased risk of MS.

Differences between children and adults with optic neuritis.

- Visual acuities at presentation may be worse (Bonhomme et al. 2009)
- More bilateral optic neuritis and optic neuritis with optic disc edema
- More optic neuritis in association with intercurrent illness
- Presentation as ADEM, a demyelinating or inflammatory event, and includes white or gray matter lesions on MRI, which is i) polysymptomatic and ii) includes encephalopathy (i.e. behavioral or mental status change) (Krupp et al., 2007). Acute disseminated encephalomyelitis (ADEM) is an autoimmune demyelinating disease that typically follows an illness or vaccination. As opposed to MS, ADEM is typically a monophasic illness that does not require long-term treatment. ADEM is more common in children than adults (Dale et al. 2000). Although patients with ADEM can present with fulminate neurologic signs and symptoms, most patients have an excellent recovery.
- More recurrent optic neuritis in children. In our study of pediatric optic neuritis (Bonhomme et al. 2009), nine patients (31%) had relapses of optic neuritis during the study period and 5 had more than one relapse.
- Neuromyelitis optica (NMO), although seen, is less common in children.
- Older age is a risk factor for development of MS.
- Postpubertal patients tend to be female and have a presentation (unilateral without disc swelling) and course similar to adults.

HORNER’S SYNDROME

Similarities between children and adults with Horner’s syndrome.

- Presentation with ptosis, miosis, and anhidrosis
- Neuro-anatomy is the same. Consideration of lesions affecting the first, second, and third-order neurons

Differences between children and adults with Horner’s syndrome.

- Congenital cases, with birth trauma in the differential diagnosis (Weinstein et al. 1980)
- More presentations with iris heterochromia
- Carotid dissection, lung cancer, and microvascular causes more common in adults.
- Need to avoid apraclonidine testing because of risk of drowsiness and unresponsiveness in young children
• Confirmation with cocaine drop testing preferred
• Neuroblastoma is a consideration, so workup should include urine vanillylmandelic acid (VMA) and homovanillic acid (HVA) testing.
• Despite opinion to the contrary (Smith et al. 2010), we believe that all patients with an obvious or confirmed Horner’s syndrome also should undergo MR imaging of the head, neck, and upper chest to rule out a responsible mass lesion. In our study (Mahoney et al. 2006), of 18 children who had complete imaging and urine studies, and the diagnosis was unknown, responsible mass lesions were found in six (33%).
• Even children with a history of birth trauma or those with Horner’s at birth (“congenital”) should be evaluated, as these patients may still harbor an underlying neoplasm (Mahoney et al. 2006)
• Caution also should be applied when hydroxyamphetamine is used in children with Horner’s syndrome. The normal development of the third-order oculosympathetic neuron and its synaptic connections depends on the integrity of the first and second neuron. In congenital preganglionic lesions, therefore, it is possible that hydroxyamphetamine will completely or partially fail to dilate the involved pupil because of transsynaptic degeneration of postganglionic fibers (Weinstein et al. 1980).
• Carotid dysgenesis is in the differential diagnosis of children with congenital Horner’s syndrome, so we also recommend MRI-angiography of the neck as part of the workup.

CME ANSWERS
1. false
2. true
3. false

REFERENCES
Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)


Ocular Myasthenia Gravis


Optic Neuritis

THE ACCESSORY OPTIC SYSTEM:
THE FUGITIVE VISUAL CONTROL SYSTEM IN INFANTILE STRABISMUS

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LEARNING OBJECTIVES
1. To review the organization of the accessory optic system
2. To review the dissociated eye movements that characterize dissociated infantile strabismus.
3. To examine the potential role of the accessory optic system in generating dissociated strabismus

CME QUESTIONS
1. Are the torsional components of dissociated eye movements in infantile strabismus modulated by visuo-vestibular pathways?
2. What subcortical visual system generates visuo-vestibular eye movements?
3. In what coordinate system is the accessory optic system organized?

KEYWORDS
1. Accessory Optic System
2. Inferior Olive
3. Cerebellar Flocculus
4. Infantile Strabismus
5. Dissociated Strabismus

INTRODUCTION
Infantile strabismus is characterized by dissociated binocular vision, which is the normal condition in lateral-eyed animals.\(^1,2\) Early binocular misalignment gives rise to dissociated eye movements (changes in eye position evoked by unequal visual input to the two eyes).\(^3\) These include latent nystagmus, dissociated vertical divergence, and dissociated horizontal deviation,\(^1,4\) all of which have a prominent torsional component. Primary oblique muscle overaction, which accompanies infantile strabismus but is not dissociated in nature, is also characterized by a torsional misalignment of the eyes.\(^4\)

These binocular deviations all correspond to normal visuo-vestibular reflexes that are operative in lateral-eyed animals.\(^1-4\) Evolutionarily, these visual reflexes antedate development of the visual cortex, which does not generate torsional eye movements in humans.\(^5\) Any attempt to anatomize infantile strabismus must therefore explain the reemergence of these atavistic reflexes, as well as their prominent torsional components. I propose that the accessory optic system, an atavistic, subcortical visual motion detection system, could generate the dissociated and nondissociated torsional eye movements that accompany human infantile strabismus.

WHAT IS THE AOS?
The AOS consists of three nuclei at the mesodiencephalic border that receive direct retinal input from the accessory optic tract (AOT).\(^6,9\) The AOT comprises an inferior and superior fasciculus, with its superior fasciculus divided into a posterior branch, a middle branch, and an anterior branch that is identical to the original transpeduncular tract (tractus peduncularis transversus) discovered in 1870 by Gudden.\(^10,11\) The number of accessory optic fibers is relatively small.\(^7\) In most mammalian species, the majority of optic fibers reach the accessory optic nuclei via the transpenduncular tract, which is visible as it courses over the brachium of the superior colliculus.\(^12\)

In most mammalian species, the AOS is composed of three paired terminal nuclei: the dorsal terminal nucleus (DTN), the lateral terminal nucleus (LTN), and the medial terminal nucleus (MTN) which receive innervation from primary optic fibers.\(^7,9\) Input to these three accessory optic terminal nuclei is predominantly from the contralateral eye.\(^7,9,11,12\) Along with the nucleus of the optic tract (NOT), these three terminal nuclei project differentially to the dorsal cap of the inferior olive,\(^13,14,15,16\) which provides the only source of climbing fibers to the flocculonodular lobe of the cerebellum.\(^7,9,14,17\) In this way, cells of the AOS converge with those of the vestibular system in the vestibulocerebellum.\(^7,9\)

Despite its name, the AOS is a primary visual system receiving direct visual information from the retina via one or more accessory optic tracts\(^13\) which are responsible for visuo-vestibular interaction in afoveate animals.\(^2,16,17\) Its retinal input is derived from ON-type direction-sensitive ganglion cells that characteristically have large receptive fields (averaging about 40 degrees vertical and 60 degrees horizontal), are direction selective, and have a preference
for slow-moving stimuli. The AOS processes information about the speed and direction of movement of large textured parts of the visual world. The accessory optic system signals self-motion as a function of slip of the visual world over the retinal surface, and generates corrective eye movements to stabilize the retinal image. As an analyzer of self-motion, the AOS subserves visual proprioception in the afoveate animal. 

The AOS is a visual system that is organized in vestibular coordinates. Experimental studies by Simpson and colleagues indicate that visual and vestibular signals which produce compensatory eye movements are organized about a common set of axes derived from the orientation of the semicircular canals. Because the AOS is directionally-sensitive to low velocity movements while the vestibular system typically responds to movements of higher velocity, the accessory optic system and vestibular labyrinths form two complementary systems to detect self motion and promote image stabilization so that objects in the visual world can be quickly and accurately analyzed.

The AOS exists in all vertebrate classes including humans, but it has been studied most extensively in the rabbit. The three preferred directions for cells in the accessory optic terminal nuclei define three directions in visual space: horizontal from posterior to anterior for the DTN, vertical up and down for the MTN and vertical down for the LTN. Its three pretectal accessory optic nuclei are closely related to the nucleus of the optic tract (NOT) and receive input predominantly from the contralateral eye. Direction-sensitive ON-type retinal ganglion cells encode retinal image slip and transmit this information to the accessory optic system, inferior olive and floccular climbing fibers, and floccular Purkinje cells. These three pairs of channels remain anatomically distinguishable within the AOS, the inferior olive and in floccular zones which, when stimulated, elicit eye movements organized in a canal-like coordinate system. Each pair conveys signals about flow of the visual surround about one of three rotations axes, which are approximately collinear with the best response axes of the semicircular canals and the rotation axes of the extraocular muscles.

The rabbit flocculus ipsilateral to the seeing eye is optimally sensitive to optokinetic stimulation about a 135 degree axis while the flocculus contralateral to the seeing eye is optimally sensitive to optokinetic stimulation around a horizontal 45 degree axis. For horizontal stimulation, the DTN and its adjacent NOT are selectively sensitive to nasally-directed optokinetic stimulation presented to the contralateral eye. Conversely, electrical microstimulation in the alert rabbit’s flocculus produces abduction of the ipsilateral eye, or dissociated torsional and vertical rotations of the two eyes corresponding to the plane of one semicircular canal. Because floccular motion detection for each eye is not fully represented on its own side of the body, monocular optokinetic responses must be derived from the synthesis of bilateral floccular representations. Thus, the flocculus provides a subcortical binocular visual system that generates asymmetrical torsional eye movements under dissociated conditions of optokinetic stimulation.

Studies using decortication have revealed contributions from the visual cortex to the AOS. Disruption of contributions from the visual cortex to the AOS by strabismus may alter the inherent biases of the accessory optic nuclei. The ipsilateral visual cortex is necessary for a number of response properties that distinguish DTN and LTN neurons in the cat from those in the rabbit. Following decortication, cat DTN and LTN neurons lose their binocularity and become nearly totally dominated by the contralateral eye. For example, LTN neurons excited by upward movement which in the cat are equal in number to those excited by downward movement, become less numerous so that the cat LTN becomes like that of the rabbit, consisting of neurons excited by slow downward movements to the contralateral eye. Unlike the LTN and DTN, neurons in the cat MTN are largely monocular and therefore similar to those in the rabbit. The monocular nasotemporal optokinetic asymmetry that characterizes infantile strabismus is known to result from monocular cortical input to the NOT/DTN, unmasking a subcortical visuo-vestibular bias that generates latent nystagmus. The AOS provides a neuroanatomical substrate whereby vertical monocular subcortical motion biases could generate the canal-based torsional eye movements that characterize primary oblique muscle overaction and DVD. Although we observe and analyze these eye movements in yaw, pitch, and roll, they are encoded in a canal-oriented, push-pull bilateral coordinate system that detects optokinetic flow in every direction.

Photic stimulation can activate the accessory optic tract in the rabbit. AOS neurons show the same responses to retinal illumination as ON-type direction-sensitive retinal ganglion cells, being excited only at the onset of retinal stimulation, and generate a firing response that is related to light intensity. This way, the AOS may implement the visuo-vestibular reflexes that characterize infantile strabismus. Since the AOS is primarily a motion detector, however, central modulation of the primitive luminance reflexes that characterize infantile strabismus may require input from other subcortical visual pathways. It is possible that other primitive luminance pathways may provide parallel subcortical luminance input to the visuo-vestibular system. Like the accessory optic system, luminance input that modulates the dorsal light reflex in fish (which corresponds to dissociated vertical divergence and primary oblique muscle overaction in humans with infantile strabismus) is transmitted to the central pretectal nucleus in the contralateral midbrain, then down to the vestibulocerebellum which integrates visual and vestibular input. These luminance and motion pathways may constitute the subcortical equivalents of the what and where visual streams within the association visual cortex. How these subcortical visual streams intercommunicate
diagnose “torsion” in the frontal plane. The accessory optic system or its target zones within the cerebellar flocculus could provide a potential template for infantile strabismus. If so, then the age-old dichotomy of Worth (congenital defect in cortical fusion) and Chavesse (early binocular misalignment) may have to be expanded to include binocular subcortical dysfunction intrinsic to the visuo-vestibular system.

CONCLUSION
The AOS is uniquely suited to generate the dissociated eye movements that characterize infantile strabismus. It is atavistic, present in humans, subcortical, crossed, sensitive to optokinetic motion, and it generates dissociated torsional eye movements (Table 1). It provides the necessary neuroanatomical substrate to process binocular visual motion in a semicircular canal-based coordinate system. The fact its retinal fibers terminate in the three nuclei of the AOT along with the adjacent NOT (a part of the pretectal nuclear complex that generates latent nystagmus) lends further credence to this hypothesis. Its fundamental role in modulating visuo-vestibular tonus suggests that it may also provide a neuroanatomical substrate for dissociated eye movements in humans with infantile strabismus. Dissociated binocular vision in infancy may unlock this atavistic visual system, generating canal-based ocular rotations that we anthropomorphize to diagnose “torsion” in the frontal plane.

Table 1: Characteristics of the Accessory Optic System

- Atavistic
- Subcortical visual system
- Crossed input from nasal retina
- Sensitive to full field optokinetic motion
- Binocular representation in the cerebellar flocculus
- Operates in a canal-based vestibular coordinate system
- Generates dissociated eye movements with torsional components
- Provides a neuroanatomic substrate for bilateral oblique muscle overaction

This analysis implies that mutations involving the accessory optic system or its target zones within the cerebellar flocculus could provide a potential template for infantile strabismus. If so, then the age-old dichotomy of Worth (congenital defect in cortical fusion) and Chavesse (early binocular misalignment) may have to be expanded to include binocular subcortical dysfunction intrinsic to the visuo-vestibular system.

CME ANSWERS
1. yes
2. accessory optic system
3. a vestibular semicircular canal-oriented coordinate system

REFERENCES


38. Schiller PH: Parallel information processing channels created in the retina. PNAS 2010;107:17087-17094.


WHAT’S NEW (AND OLD) IN OPTIC NERVE HYPOPLASIA

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LEARNING OBJECTIVES
1. The attendee will be able to understand the historical confusion that led to the inappropriate significance of absence of the septum pellucidum.
2. The attendee will be able to identify key clinical associations commonly found in patients with optic nerve hypoplasia.
3. The attendee will be able to describe the appropriate work-up and follow-up of patients with optic nerve hypoplasia.

CME QUESTIONS
1. True or false? Patients with ONH and normal septum pellucidum do not need endocrinology evaluation.
2. Which endocrinopathies have been documented to evolve post-natally in children with optic nerve hypoplasia?
3. True or false? Children with unilateral ONH are at high risk for endocrinopathy and developmental delay.

KEYWORDS
1. Septo-Optic Dysplasia
2. Hypopituitarism
3. MRI
4. Hypothalamus
5. Corpus Callosum

INTRODUCTION
Optic nerve hypoplasia has been recognized as a leading cause of childhood blindness, and its association with hypopituitarism has been known for four decades. It has more recently been recognized that the majority of the systemic problems associated with ONH are due to dysfunction of the hypothalamus and cortical miswiring. Absence of the septum pellucidum is not associated with the major neurologic or systemic consequences, and in general, MRI scans or laterality of disease cannot be used to predict hypothalamic dysfunction.

Review of the literature reveals that de Morsier, who coined the term, “septo-optic dysplasia” was not referring to ONH, and in fact, never described a case of ONH. When referring to ONH, the terms, septo-optic dysplasia and de Morsier’s syndrome, are historically inaccurate and diagnostically misleading.

This review will summarize the state of knowledge on optic nerve hypoplasia and reanalyze the historical literature that led to misunderstandings of its association with neurologic or endocrinologic abnormalities. The case will be made for abandonment of the terms, septo-optic dysplasia and de Morsier’s syndrome.

PREVALENCE
Optic nerve hypoplasia (ONH) has been recognized as an increasingly frequent cause of congenital blindness affecting one or both eyes. In 1997, bilateral ONH surpassed retinopathy of prematurity as the single leading cause of infant blindness in Sweden. Only cortical visual impairment of multiple etiologies was more common than ONH in blind children. The prevalence of ONH in Sweden quadrupled between 1980 and 1999 to 7.1 per 100,000, while all other causes of childhood blindness declined as diagnoses from the same major ophthalmic center. In 2006, the prevalence of ONH in England had risen to 10.9 per 100,000 children.

Owing to incomplete registries of blindness, the prevalence of ONH in North America is unknown. Prior to 1970, it was considered rare. In fact, prior to 1962, only one case had been diagnosed in British Columbia, but 20 cases were subsequently diagnosed by 1974, for an estimated prevalence of 1.8 per 100,000. Acer noted a similar increase in incidence of reported cases in the 1970s. ONH was identified in 12% of blind infants in Harris County in Texas in the early 1980s. Surveys of schools for the blind in the United States in 1999 revealed that ONH accounted for 5.7% to 12.9% of blind students. Such surveys underestimate the actual prevalence, because cognitive or behavioral impairments exclude most children with ONH from schools for the blind. In 2007, the Babies Count registry reported ONH as the third most prevalent cause (behind cortical vision impairment and retinopathy of prematurity) of any vision impairment in children age three years or younger in the United States. Of all conditions, ONH was the most likely to cause legal blindness.
HISTORICAL DESCRIPTIONS

The first description of ONH is generally ascribed to Magnus in 1884, but the first artistic rendering of the optic disc appearance was by Schwarz in 1915. The first recognition of an association of ONH with agenesis of the septum pellucidum was by Dr. David Reeves at Children's Hospital Los Angeles, in 1941.

The purpose of Reeves report was to demonstrate the youngest case of agenesis of the septum pellucidum diagnosed by air encephalogram. The 4-month-old patient was coincidentally blind, and examination under anesthesia by Dr. S. Rodman Irvine revealed “bilateral primary optic atrophy of undetermined origin, probably, however, on the basis of a congenital aplasia.” Dr. Irvine was a famous member of a prominent ophthalmological family in Southern California, and was also the first to describe the association of cystoid macular edema with cataract surgery.

The association of ONH with absence of the septum pellucidum was later erroneously attributed to Georges de Morsier, who did, indeed, coin the term “la dysplasie septo-optique (septo-optic dysplasia).” However, the “optic dysplasia” recognized by de Morsier was not ONH. In his treatise on cranioencephalodysraphism, his third chapter highlighted his fascination with absence of the septum pellucidum that had incidentally been noted in post-mortem brains. From his post-mortem collection of brains with absent septum pellucidum, he discovered that one brain had a unilaterally vertically rotated optic tract. This was from a woman who died of pyelonephritis at the age of 84 years without any history of vision problems. He also described the case of a living 44 year-old alcoholic man who had “slight narrowing of the visual field with enlargement of the blind spot,” but was incidentally discovered to be missing the septum pellucidum on air encephalogram. De Morsier supplemented these two cases with 34 others (11 autopsy cases and 23 radiographic cases) from the literature that had agenesis of the septum pellucidum, eight of which had some other eye or optic nerve problem. These included one case of bilateral anophthalmous; three cases of bilateral optic atrophy (one with Apert’s Syndrome, and one with osteogenesis imperfecta); three cases of unilateral optic atrophy (two systemically normal and one with hemiparesis and mental retardation). The only case with definite ONH from the literature cited by de Morsier was the case that had been previously documented by Reeves. It was from this compilation of disparate cases that an association of eye problems with agenesis of the septum pellucidum (i.e. septo-optic dysplasia) was postulated.

De Morsier believed that agenesis of the septum pellucidum and various ocular anomalies were “not fortuitous” associations. He hypothesized that the septum pellucidum served to connect the corpus callosum to the fornix, and that lacking this supporting structure resulted in penetration of the chiasm by the third ventricle. This malformation of the chiasm then somehow led to optic nerve or ocular anomalies.

Three years following de Morsier’s report, Gross and Hoff reported their autopsy findings from 465 brains from patients with severe neurologic problems or systemic malformations. They identified thirteen brains with absence of the septum pellucidum. One of these had bilateral ONH, and seven (six bilateral; one unilateral) had optic atrophy. They also identified 12 cases of partial or complete corpus callosum agenesis. Two of these had microphthalmos with bilateral optic atrophy and one had unilateral ONH.

Thus, prior to 1970 only two cases of ONH associated with absence of the septum pellucidum had been described in the medical literature, and neither of these had been identified by de Morsier.

In 1970, Ellenberger and Runyan described a case of unilateral ONH, absent septum pellucidum and dwarfism in a 23-year-old woman. Dr. William Hoyt, who nearly simultaneously wrote the landmark report that recognized the association of ONH with growth hormone deficiency, predicted the absent septum pellucidum in Ellenberger and Runyan’s case. In their paper Hoyt et. al. described nine patients with ONH and pituitary dwarfism, four of whom were missing the septum pellucidum. They generously, but erroneously, attributed the association of ONH and agenesis of the septum pellucidum to de Morsier, and resurrected the term “septo-optic dysplasia,” which is now commonly referred to as de Morsier’s Syndrome. “Hoyt’s Syndrome” would be a more appropriate eponym, particularly since the association of ONH with hypopituitarism, not septum pellucidum agenesis, is the clinically important revelation.

De Morsier would scarcely have recognized the attribution to himself. He was trained as a psychiatrist in Geneva under de Clérambault. Lacking a suitable neuropathologist replacement after the death Edouard Long, de Morsier was enjoined to lecture in neuropathology one hour per week starting in 1933 during which time he attempted to catalogue the various craniodysraphisms. Ultimately he was appointed head of neurology in 1960, a position at which he served until his retirement in 1964. Arguably, de Morsier’s greatest contribution to medicine was his description of the Charles Bonnet Syndrome, which he named after the nineteenth century naturalist, who in 1760, had documented the visual hallucinations of his grandfather. There is no record of de Morsier ever identifying a case of optic nerve hypoplasia.

RADIOGRAPHIC CORRELATES

SEPTUM PELLUCIDUM

Following the resurrection of “septo-optic dysplasia” by Hoyt et. al., absence of the septum pellucidum garnered inappropriate dogmatic significance. Its association with pituitary dysfunction was documented in retrospective studies hampered by ascertainment bias. Other studies refuted the association, even to the point of showing no association of any adverse outcome with agenesis of the septum pellucidum. Indeed, as with de Morsier’s
experience, most cases of agenesis of the septum pellucidum are coincidentally detected and not associated with optic nerve or hormone problems. The prevalence of absent septum pellucidum in the general population is unknown. In the only prospective study of ONH, absence of the septum pellucidum was not associated with laterality of ONH, vision, pituitary dysfunction, or developmental outcome.\textsuperscript{25,26}

Nonetheless, the term, septo-optic dysplasia (SOD), has persisted and its definition has evolved to include midline brain abnormalities such as hypoplasia of the corpus callosum or pituitary anomalies on magnetic resonance imaging (MRI), in addition to absent septum pellucidum. This definition has served to focus investigators on morphogenetic mechanisms for the condition. It disregards the fact that a small corpus callosum frequently denotes hemispheric disease, and that most neuroradiographic abnormalities associated with ONH are not midline.\textsuperscript{26} These include hydrocephalus, white matter hypoplasia, cortical heterotopia, pachygria, schizencephaly and arachnoid cysts. Rather than reassessing the appropriateness of the nomenclature, investigators recognizing these non-midline findings simply expanded the terminology to include “SOD plus” as a more severe expression on the spectrum of ONH.\textsuperscript{27}

CORPUS CALLOSUM

Corpus callosum hypoplasia is the most prevalent neuroimaging abnormality associated with ONH. It is commonly associated with absence of the septum pellucidum; however, absence of the septum pellucidum cannot serve as a surrogate for corpus callosum hypoplasia, as partial agenesis of the corpus callosum may not be associated with absence of the septum pellucidum. Corpus callosum hypoplasia has been associated with developmental delay, but not with hypopituitarism in children with ONH.\textsuperscript{26}

Corpus callosum hypoplasia is detected in 1.8-2.05/10,000 live births and in 2.3% of developmentally disabled individuals.\textsuperscript{28,29} Forty-nine percent of patients with corpus callosum hypoplasia have other central nervous system abnormalities, including non-midline defects typically associated with ONH (cortical heterotopias, schizencephaly, white matter hypoplasia, polymicrogyria).\textsuperscript{28} However, ONH occurs in less than 10% of children with corpus callosum hypoplasia.\textsuperscript{29} Corpus callosum hypoplasia is associated with a myriad of syndromic conditions and chromosomal abnormalities, but pituitary dysfunction in those without ONH is uncommon.\textsuperscript{30} Although both ONH and corpus callosum hypoplasia may be the consequence of more generalized problems with CNS development, the presence of ONH appears to be uniquely associated with hypothalamic dysfunction.

PITUITARY GLAND

Pituitary abnormalities on neuroimaging include empty sella, non-visualized infundibulum, ectopic posterior pituitary, and non-visualized posterior pituitary. These radiographic findings occur in 13-34% of children with ONH, and nearly all of those have hypopituitarism.\textsuperscript{26,31} However, hypopituitarism occurs in 75% of patients with ONH, the majority of whom have no pituitary abnormalities on neuroimaging. It is also interesting that absence of the posterior pituitary bright spot on T1-weighted MRI has been reported to be associated with anterior pituitary function.\textsuperscript{31} but most of those patients do not have diabetes insipidus, as would be expected if the vasopressin granules that cause T1-weighted hyperintensity are actually missing.\textsuperscript{32}

OPTIC NERVE

Attempts to diagnose ONH based on radiographic measurements of the optic nerve or chiasm have been promising.\textsuperscript{33,34} Such studies have been retrospective, lacked controls with normal and atrophic optic nerves, or failed to adjust for age in young patients. Nonetheless, it seems likely that high-resolution MRI could be used to distinguish ONH from optic atrophy once the appropriately controlled studies are done. Assessment of the intracranial portion of the optic nerves is more reliable for detecting ONH than assessment of the orbital component.\textsuperscript{35}

CLINICAL DIAGNOSIS

The diagnosis of ONH is made by ophthalmoscopic confirmation of a small optic disc. Such confirmation may be difficult with the binocular indirect ophthalmoscope due to limited magnification. With inadequate resolution, small pale optic discs may be difficult to distinguish from a surrounding hypopigmented scleral canal, and therefore misdiagnosed as normal size discs with optic atrophy. The optimal method for diagnosing ONH in a young child is with direct ophthalmoscopy, especially if the diagnosis is not clear by indirect ophthalmoscopy. Direct ophthalmoscopy is usually not difficult in visually impaired children as they have minimal objection to the light or to the proximity of the examiner, as long as the examiner does not touch the child’s face.

Many authors have suggested that ONH can be confirmed with measurements of the optic disc from fundus photographs. Most have relied on measurement of disc diameter or area relative to other retinal landmarks. In all series of normal children, the ratio of the horizontal disc diameter (DD) to the distance between the macula and the temporal edge of the disc (DM) has been greater than 0.35.\textsuperscript{25,36,37} DD/DM ratios less than 0.35 crudely correlate with vision outcomes.\textsuperscript{38} Although most patients with DD/DM ratios less than 0.35 have generally been described as having ONH, some with DD/DM ratios of 0.30 to 0.35 also had normal vision. Some overlap in optic disc size between normal and ONH is not surprising. Although the absolute risk for systemic complications in these borderline cases has not been determined, it is clear that some have associated hypopituitarism, so they should not be dismissed as normal without appropriate investigation.

The average DD/DM ratio of preterm, but otherwise normal, infants was 0.26 at birth, according to De Silva et al.\textsuperscript{39} Compared with measurements from adults made by other researchers, they estimated that the DD increases 44% in a lifetime, compared to increases in DM of only 11%. This
results in increased DD/DM ratio with age, which presumably occurs in the first 2 years of life, concomitant with maximal growth of the eye. Therefore, the age of the patient may need to be considered when measuring DD/DM ratios.

Thus far attempts to diagnose ONH or predict vision outcomes from other imaging modalities such as optical coherence tomography (OCT) have not been reported. Eyes with ONH may have a poorly developed foveal umbo on OCT in spite of otherwise normal appearing foveae on ophthalmoscopic examination. The foveolar thickness is normal, but absence of the ganglion cell and nerve fiber layers results in a retina of uniform thickness in which the umbo cannot be distinguished with OCT. Presumably eyes with ONH and a visible foveal umbo could be anticipated to have good vision.

For practical purposes, fundus imaging is not necessary to diagnose ONH. An experienced clinician should be able to assess the area of the disc relative to the area of the central retinal vessels overlying it.

In cases of ONH, a ring of hypo- or hyperpigmentation often surrounds the disc defining the area of the putative scleral canal. This is presumably caused by migration of sensory retina and pigment epithelium from their original margin at the edge of the optic stalk to a new position at the border of the optic nerve that failed to fill, or regressed from, this area. This “double ring” sign does not define ONH, as a similar appearance may be present in myopia or other common conditions.

Tortuous retinal arterioles, venules, or both, may accompany ONH. Alternatively, the vessels may be uncommonly straight with decreased branching. Such a nonbranching vessel pattern has also been recognized in children with primary growth hormone (GH) deficiency. It is not known if the anomalous vascular patterns in ONH correlate with the endocrine dysfunction.

ONH has been broadly defined by some to include any optic disc with congenitally decreased neuronal area. As such, those eyes with a normal sized optic discs, but with enlarged cups, would qualify as having ONH. Such an appearance typically occurs in premature infants with periventricular leukomalacia. Although such optic nerves may have fewer than the normal number of axons and be technically hypoplastic, these children are not at risk for the same developmental and endocrinological consequences as children with more typical of ONH. They should, therefore, not be considered in the same diagnostic category.

Similarly, eyes with major congenital malformations such as microphthalmous, large colobomas, or persistent hyperplastic primary vitreous might be expected to have small optic nerves. Although occasional patients with bilateral ONH have been seen with major malformations in one eye, a diagnosis of ONH should not be made on the basis of small optic nerves in eyes affected with other major malformations.

Finally, a unique congenital disc anomaly known as superior segmental optic nerve hypoplasia or “topless disc syndrome” presents as an incidental finding on routine eye examination in children or adults. This is nearly always associated with a history of maternal diabetes during gestation. Such optic discs appear to have the top one-third of the disc missing resulting in inferior visual field defects, but normal visual acuity. Affected individuals do not have increased risk for any of the neurologic or systemic consequences of ONH, and should not be considered to be the same condition.

VISION

Most children with ONH initially present with vision problems. Nystagmus usually develops at 1 to 3 months of age followed by strabismus, typically esotropia, in the first year of life. Children with markedly asymmetric or unilateral ONH may present primarily with strabismus rather than nystagmus. Patients with relatively symmetric hypoplasia may have asymmetric vision from superimposed amblyopia due to strabismus or anisometropia.

Approximately 80% of children with ONH are bilaterally affected and two-thirds of those are asymmetrically affected. The unilateral cases are usually detected at a later age than those bilaterally affected. Children with unilateral ONH are at risk for hypothalamic/pituitary dysfunction (69%) and developmental delay (39%), although that risk is significantly lower than those bilaterally affected (81% and 78%, respectively).

Visual acuity ranges from no light perception to near normal. More than 80% of bilateral cases are legally blind. Most affected children enjoy some improvement in their vision in the first few years of life. It is possible that improved axonal function due to optic nerve myelination that occurs in the first 4 years of life is responsible for this benefit. Although subjective improvement in visual behavior is common, it is difficult to quantify vision improvement in this age group. However, improvement from only light perception behavior to quantifiably functional vision is not rare.

HYPOTHALAMIC DYSFUNCTION

Hypothalamic dysfunction is the most common nonvisual problem in patients with ONH, and results in loss of regulation of homeostatic mechanisms controlling behavior and pituitary gland function.

HYPOPITUITARISM

In most cases of ONH, hypopituitarism is believed due to hypothalamic dysfunction rather than pituitary dysgenesis. Thus children with ONH and hypopituitarism usually have moderately elevated serum prolactin levels, as this hormone is normally suppressed by the hypothalamus. Hypopituitarism was notably uncorrelated with laterality of ONH in a prospective study from which only 7% of subjects were referred by endocrinologists; thus with limited ascertainment bias for hypopituitarism. Growth hormone (GH) deficiency was the most common endocrinopathy (70%), followed by hypothyroidism (43%), adrenocorticotropic hormone (ACTH)
deficiency (27%), and diabetes insipidus (5%). This high prevalence of endocrinopathy is consistent with previous retrospective studies.\textsuperscript{47,48} Delayed or precocious puberty is common, but the incidence is unknown.

The incidence of evolving pituitary dysfunction in children with ONH is not currently known, but cases of acquired hypopituitarism have been reported.\textsuperscript{48,49} Thus, the absence of a particular pituitary endocrinopathy does not imply absence of future pathology.

**THIRST/HUNGER**
Ventromedial nuclei within the hypothalamus suppress hunger and eating in response to leptin, whereas lateral hypothalamic nuclei stimulate feeding behavior and regulate metabolism.\textsuperscript{50} Thus, children afflicted with ONH frequently exhibit hyperphagia with obesity or hypophagia, with or without wasting. Some children also have an aversion to certain textures of food. Water-seeking behavior (and consequent enuresis) is also common and may be mistakenly attributed to diabetes insipidus.

**SLEEP**
The biological clock is generated within the suprachiasmatic nuclei of the anterior hypothalamus above the optic chiasm. They receive photic information via the optic nerves to synchronize the clock to the 24-hour light-dark cycle. It is necessary to reset the circadian pacemaker each day with visual stimulation.\textsuperscript{51,52,53} Disturbance of the circadian system can have significant, pernicious effects on physiology and behavior.\textsuperscript{54,55} Many children with ONH have primary clock lesions with loss of rhythmicity and sleep or wakefulness distributed over the 24-hour day.\textsuperscript{56,57} Alternatively, they may have inadequate retinohypothalamic input to daily entrain the circadian clock, resulting in free-running sleep-wake cycles asynchronous with other family members. In either case, such sleep irregularities commonly result in behavioral difficulties and disruption to family life.

**TEMPERATURE REGULATION**
The medial preoptic region of the hypothalamus is involved in fine body temperature regulation and, through communication with the paraventricular nucleus, regulates fever response.\textsuperscript{58} It is therefore not surprising that many infants and children with ONH have problems with body temperature regulation and may be frequently hospitalized to rule out sepsis.\textsuperscript{59}

**DEVELOPMENTAL OUTCOMES**
Margalith et al. in 1984 were the first to report developmental delays in ONH, estimating neuropsychological handicaps in nearly three-fourths of cases of ONH.\textsuperscript{60} Burke et al. estimated delayed development, based on neurologic examination, at a similar frequency.\textsuperscript{61} Observations of developmental delay in association with ONH range from isolated focal defects to global delay.\textsuperscript{62,63} Garcia-Filion et al. found developmental delays in 71% of ONH patients using standardized neuropsychological instruments in a prospective study.\textsuperscript{64} Motor delays were the most common (75%) and communication delays were the least common (44%). Independent risk factors for significantly delayed cognitive and overall development included hypoplasia of the corpus callosum and hypothyroidism, but not absence of the septum pellucidum. Developmental delay occurred in unilateral (39%) as well as bilateral (78%) cases of ONH.

Autism spectrum disorders are over-represented in the visually impaired population, with prevalence estimates up to 25% in children with severe vision impairment.\textsuperscript{65} The prevalence of autism appears even higher children with ONH. A group of thirteen Swedish children with ONH and blindness, six had autism and three had an “autistic-like” condition.\textsuperscript{66} Parr et al. reported that, in a sample of 83 children with ONH and moderate to severe vision impairment (worse than 6/30), 37% (31/83) had social, communicative and repetitive or restricted behavioral difficulties and the majority of those (26/31) had a clinical diagnosis of autism spectrum disorder.\textsuperscript{67} Precise prevalence estimates of autism require modifications of the autism diagnostic instruments for visually impaired subjects. Such modifications have not yet been validated.

**PATHOGENESIS AND GENETICS**
The presumed association of midline cerebral defects with ONH has led to a focus on the genetic mechanisms involved in division of the prosencephalon into cerebral hemispheres and in formation of the pituitary gland. Thus, several candidate genes have been identified as responsible for cases of “SOD.” These include mutations of HESX1 associated with holoprosencephaly and SOX2 associated with anterior pituitary hypoplasia and hypogonadism. Only five cases of ONH in humans have ever been associated with the HESX1 mutation.\textsuperscript{67,68} Some of these were seen in cases of severe forebrain malformation, such as alobar holoprosencephaly.\textsuperscript{69} Such major malformations would be expected to impact the development of subsequent structures such as the optic nerves, corpus callosum and septum pellucidum. However, the vast majority of cases of ONH cannot be attributed to specific mutations. In fact, less than 1% of cases of ONH in large series were found to have an HESX 1 mutation and none were found to have SOX2 mutations.\textsuperscript{70,71}

The dearth of families with more than one affected child and the lack of substantiated reports of trans-generational transmission argue against a hereditary cause for most cases of ONH. Fundus photographs from the only multigenerational report are not convincingly representative of ONH.\textsuperscript{72} There have been no reports of affected identical twins.

**PRENATAL RISK FACTORS**
Lack of definitive genetic associations has led to a search for prenatal environmental or biological risk factors for development of ONH. Nearly all prenatal associations with ONH originate from retrospective review of records or anecdotal reports. The most commonly reported associations include young maternal age and/or primiparity\textsuperscript{60,68,70,73,74} maternal use of recreational drugs (eight total cases).\textsuperscript{34,65,70,75,76}
anticonvulsants (nine total cases), antidepressants (three total cases), and viral infections during pregnancy (four total cases). In small case series, ONH has been reported in 25-48% of children with fetal alcohol syndrome, but in large series of near-consecutive cases of ONH, any prenatal alcohol exposure was reported in 6-33%, and there were no reports of excessive prenatal alcohol consumption.

Only two studies have systematically and sequentially investigated prenatal correlates in large cohorts of patients with ONH. The first was a case-control study of 100 severe bilateral cases in Sweden, and data were obtained from interviews conducted in the first trimester of pregnancy by a variety of midwives. That data has the advantage of being relatively unbiased by recall or pregnancy outcomes, but the disadvantage of not capturing associations that may have occurred after the interview. That study found increased risk with young maternal age, primiparity, and early prenatal smoking exposure, but not with drug or alcohol exposure.

The second study used a post-natal questionnaire and compared exposures with national registry data from pregnant women during the same period of time. This study confirmed that young maternal age and primiparity were independent risk factors, but refuted an association with tobacco, alcohol, or drug exposure. In addition, it suggested pre-natal maternal weight loss or poor weight gain, and premature labor (without premature birth) as additional risk factors. There was no association with gestational diabetes mellitus, as has been reported for the "topless disc syndrome."

MANAGEMENT

Since ONH is particularly associated with abnormal hypothalamic function, physicians should be vigilant for signs of hypothalamic dysfunction along with any vision problems in children and vice-versa. Therefore, all neonates with jaundice and recurrent hypoglycemia should have ophthalmoscopic evaluation, especially if associated temperature instability. Similarly, all infants with poor visual behavior, strabismus, or nystagmus by three months of age should have an ophthalmoscopic examination to rule out ONH.

Once ONH is confirmed ophthalmoscopically, MRI of the brain should be obtained. The MRI can rule out treatable conditions such as hydrocephalus but can also be used to anticipate developmental delay associated with corpus callosum hypoplasia or other major malformations. Major malformations such as schizencephaly or polymicrogyria should prompt neurologic examination in anticipation of focal deficits or seizures. In the past MRI of the brain was used to identify absence of the septum pellucidum in order to determine the need for endocrinologic evaluation. This feature can now be disregarded, as all children with ONH regardless of the septum pellucidum status need pituitary function evaluated.

Endocrinologic work-up should include fasting morning cortisol and glucose, thyroid stimulating hormone, free T4, and the growth hormone surrogates - insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3). If the child is less than 6 months of age, leuteinizing hormone, follicle-stimulating hormone, and/or testosterone levels should be checked in order to anticipate delayed sexual development. Beyond 6 months of age, sex hormones are not normally produced until puberty, and thus cannot be tested. Micropenis, also a harbinger of delayed puberty, can be treated with testosterone injections during infancy.

Children should be monitored at least semi-annually for growth. With growth deceleration, thyroid function tests should be repeated and provocative testing for cortisol should be performed. These should also be done if IGF-1 or IGFBP-3 is low, even if the child is growing normally. Free T4 should be rechecked at least semi-annually until two years of age and annually thereafter until at least four years of age.

If fasting morning cortisol is low, it should be repeated or provocative testing for cortisol should be done. This can often be done simultaneously with GH testing, using glucagon as the provocative agent. Children with inadequate cortisol response to provocative tests should be given both oral and injectable forms of glucocorticoids for administration during illness or physical stress.

Occupational, physical, and/or speech therapy are frequently needed by children with ONH. Attention should especially be given to early development of oral motor skills and acclimation to textured foods for those children resistant to eating. Incorporating dialogue into song can sometimes ameliorate delayed verbal communication.

Children with autistic behaviors should be evaluated by a neuropsychologist skilled in autism assessment as well as experienced in dealing with visually impaired children. Lacking such experience, the autism expert should enlist assistance from a teacher for the visually impaired to appropriately modify the testing instruments.

Sleep dysregulation can sometimes be alleviated by entraining the circadian clock with low doses (0.1–0.5 mg) of melatonin in the evening or, alternatively, with soporific doses (3–5 mg) at bedtime.

The vision of young children with ONH should be monitored at least annually, and any refractive errors should be treated when the visual acuity reaches a functional level. Patching of the better eye can result in improvement of vision in the worse eye. However, if the ONH is asymmetric, maintenance of improved vision requires prolonged patching that can be disruptive to development in a child with many other handicaps. Thus, amblyopia therapy should be reserved for those cases in which the potential vision in each eye is felt to be fairly good. Children with unilateral or markedly asymmetric ONH should not be treated with patching.
Early surgical correction of strabismus should be reserved for children who have symmetrical functional vision in the eyes, and thus some potential for binocularity. Otherwise, correction of strabismus should be deferred until it is an impending psychosocial issue.

CONCLUSION

Optic nerve hypoplasia is an increasingly prevalent, probably non-hereditary, cause of congenital blindness that is the unifying feature of a syndrome that usually includes developmental, hypothalamic and/or neuro-anatomical abnormalities. The first recognized association was with development, hypothalamic and/or neuro-anatomical abnormalities. The presence of ONH alone imparts risk for serious systemic and neurologic problems that need to be carefully monitored. Focus on the septum pellucidum has distracted physicians from the serious implications of the syndrome. “Septo-optic pellucidum has distracted physicians from the serious implications of the syndrome. “Septo-optic dysplasia” and “de Morsier’s syndrome” are inappropriate and complicated nature of the syndrome.

CME ANSWERS

1. false
2. central hypothyroidism; adrenal insufficiency
3. true, but at less risk than those with Bilateral ONH.

REFERENCES


WHY JUVENILE PILOCYTIC ASTROCYTOMA OPTIC PATHWAY GLIOMAS ARE HAMARTOMAS

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LEARNING OBJECTIVES

1. That Grade I juvenile pilocytic astrocytomas (optic gliomas) are self-limited growths which meet all criteria for designation as hamartomas.

2. Anti-mitotic regimens, both ionizing radiation therapy and genotoxic chemotherapy have failed to show any efficacy. By failing to stratify “optic pathway gliomas (OPG)” or “low-grade gliomas (LGG)” into Grade I and Grade II tumors, and by assuming that an initial decline in visual acuity is indicative of an enlarging tumor necessitating treatment when the opposite may be the case, published results have had little relevance.

3. Intracranial and intraorbital optic gliomas should be treated in much the same way as those which occur intraocularly.

CME QUESTIONS

1. Are optic pathway gliomas or low grade gliomas synonymous with Grade I, juvenile pilocytic astrocytomas, commonly referred to as optic gliomas?

2. Does the term hamartoma indicate stability and lack of growth during development?

3. Does a decline in visual acuity indicate that an optic glioma is growing?

KEYWORDS

1. Hamartoma
2. Non-Stratified Data
3. Collins’ Law
4. Mucosubstance
5. Natural History Optic Glioma

It is important to recognize that many optic pathway gliomas (OPG) do represent neoplasms, since OPGs are defined as a collection of both pilocytic WHO Grade I as well as fibrillary WHO Grade II and higher tumors. Bill Hoyt along with Leroy Meshel, Simmons Lessell, Norman Schatz, and Rod Suckling were among the first, in 1973, to define such neoplasms affecting the visual pathways.1

This presentation, however, shall only specifically address the behavior of Grade I juvenile pilocytic astrocytomas, those more commonly referred to as optic gliomas. Grade II and higher malignant gliomas of the anterior visual pathway that behave more aggressively, including glioblastoma multiforme, are recognized in adults 1,2 and may occasionally also occur in children; 3,4,5,6 their diagnosis and treatment, altogether different, is not discussed here.

Optic gliomas (World Health Organization grade I pilocytic astrocytomas) do, of course, represent tumors.7 Such terminology, however, while technically correct, remains imprecise and can be misleading. The normal crystalline lens of the eye, for example, also represents a tumor, yet to call it so with patients would unquestionably lead to irresponsible and inappropriate interventions.8

The situation with juvenile pilocytic gliomas is not entirely dissimilar. By alluding to these masses simply as tumors, or by including them within categories such as “OPG” (optic pathway gliomas) or “LGG” (low-grade gliomas) which are inclusive of frank neoplasms such as Grade II fibrillary gliomas, one leads both family members and physicians alike toward antimitotic and genotoxic therapies that, to date, have had no proven efficacy.8, 9, 10, 11,12,13, 14, 15, 16, 17, 18 The term neoplasm, which commonly implies a more general and uncontrolled status of cellular proliferation, with active mitoses, does not apply to these developmental lesions, many of which remain stable and asymptomatic, or regress (when they ever do actually grow, it is only during the period of development, hence the adjective “juvenile”). Whether benign or malignant, the word neoplasm literally means a new growth, from the Greek neo-, new + plasma, that which is formed, or a growth = a new growth. Most optic gliomas, on the other hand, represent congenital lesions that remain stable; i.e., they are not new and do not grow.

The terms hamartoma and choristoma were created by Albrecht 19, 20 in 1904, to designate tumors that had the potential to grow in self-limited form during the period of development. Hamartoma signifies a disorganized overgrowth of differentiated tissue normal to a site, while choristoma indicates such growth when it is ectopic to the organ location. This terminology has been used, without controversy, to describe the evident growth of optic disk and retinal glial hamartomas in tuberous sclerosis, or of the melanocytic iris hamartomas known as Sakurai-Lisch nodules in NF1.
Choristomas, such as dermoids, may certainly also enlarge, often via the accumulation of mucosubstance or glandular secretions. The notion that gliomas represent relatively stable congenital growths was first hinted by Hudson in 1912.21 Histopathologists, notably Davis 22 and to some extent Zimmerman 23 described the essentially hamartoma-like qualities of these tumors in their written correspondence. These gliomas were openly declared to have the features of congenital hamartomata by Hoyt and Baghdassarian in 1969,24 and later by Borit and Richardson 25 who also espoused this opinion. The previous inability to monitor juvenile pilocytic astrocytomas intracranially, however, and the more serious consequences that could entail from enlargement within the limited cavitory space of the skull, understandably led to difficulties in ascertaining their self-limited growth pattern and hesitancy amongst some to call them hamartomas. Subsequent rare descriptions, beginning only in the 1970s, of apparent anaplastic transformations also served to undermine these notions.

The more recent advent of neuroimaging has, however, confirmed only occasional growth during the period of development, along with the possibility for spontaneous regression. Most growth, furthermore, has been related to microcystic collections of mucosubstance and hydration, 9, 26 not proliferation of a solid tumor component. 27

Growth of the solid tumor portion of gliomas is a function of both cellular proliferative and apoptotic activity; both may be high, or both low, reflecting a steady-state function within a tumor that demonstrates clinical stability. 28, 29 For these reasons, histopathological examinations assessing proliferative activity alone using immunohistochemical labeling indices, such as MIB-1 to detect Ki-67 protein associated with cells during their proliferative phase, 5, 53 without also ascertaining the rate of apoptosis, cannot provide information of prognostic utility. 8, 31 Inherently limited biopsy sampling sizes for tumors that are known to be heterogenous both in their composition and in their growth patterns and phases, further limits the prognostic potential for such approaches.

By definition, Grade 1 pilocytic gliomas possess only rare, if any, mitotic figures and the majority of tumors demonstrate overall stability 5, 24, 32 with only limited growth potential during development. Unlike higher grade gliomas, they do not show p53 mutations. 28 and no genetic changes typically associated with the more clinically aggressive fibrillar astrocytomas have been found in these masses. 33, 34

On the other hand, spontaneous regression may also occur, 31 and once a tumor is discovered, it is as likely to shrink given enough time, as it is to grow initially. 13, 16, 17, 18, 31, 35 Although as many as 25% of children with NF1 have gliomas, 36, 37, 38, 39 such incidences have not been noted in adults with NF1, and virtually no new cases present in adults with, or without, NF1. These studies and others 37, 40, 44 have also indicated or shown T2-weighted signal abnormalities at some point in as many as 80% of patients with NF-1. The fact that both T1- and T2-weighted MRI signal abnormalities in NF-1 patients disappear later in life is indicative that a process of spontaneous glial regression must be widespread. 40, 44 Spontaneous regression is often overlooked in patients known to harbor an optic glioma whose clinical condition has remained stable for many months or years and for whom repeat scans are not performed, or for whom the older scans are no longer available for comparison. Since first reported by Bzowski and colleagues in 1992, 46 it is being noted with increasing frequency. The personal experience of virtually all those who have reported instances of MRI-documented spontaneous regression has been to subsequently identify further cases in their practices.

Mechanisms, such as programmed cell death (apoptosis) outpacing proliferation of cells may be involved. Given that the proliferation of juvenile pilocytic astrocytoma cells slows down with age, 47 it is plausible to think that given enough time, and the patient ability to endure its presence, most such tumors would eventually regress. The well-established fact that recurrences following surgery of these Grade I masses, unlike that for Grade II and higher tumors, do not follow Collins’ law of exponential growth patterns as a function of patient age, is also indicative of this. 11, 48

No consensus exists regarding the criteria for classifying pilocytic astrocytomas with atypical features. However, many features indicated by some authors, such as hyperchromasia, multinucleated cells, microvascular proliferation, necrosis, increased cellularity, and even at times a higher than usual rate of mitosis, in general, are not accepted by histopathologists to be associated with anaplasia or malignancy. Some of these features merely represent degenerative atypia seen more often with aging, while other features have no proven relationship with malignant behavior or survival. 23, 25, 49, 52

Misleading terminology is also sometimes used to describe mostly adult and Grade II and higher gliomas as “pilocytic-like”, “atypical pilocytic”, or “pilocytic with anaplastic features” 5, 53 causing many to erroneously believe an anaplastic transformation of Grade I tumors into a higher grade neoplasm occurred.

A recent review of the literature, however, revealed that all individuals who suffered actual anaplastic transformation all had had tumors that had been irradiated years before. 53, 54 Such anaplastic degenerations of Grade I pilocytic astrocytomas, the first cases reported in the 1970s, were therefore all iatrogenic in origin while spontaneous anaplastic degeneration does not occur. 51 As early as 1937, the possibility of radiotherapy inducing malignant transformation of astrocytomas had been raised by Tarlov, 55 with others later also voicing similar concerns. 56-58

Gliomas also do not metastasize in the usual sense; during infancy, rarely, “drop metastases,” often asymptomatic in nature, may occur to the leptomeninges.
via the cerebrospinal fluid passageways after surgical manipulations during ventricular shunt placement, or less commonly, after hemorrhagic cystic degeneration and rupture. 9,26,82 Much as occurs with such acknowledged intraocular hamartomas such as astrocytic or glial tumors of the optic disc or retina 63-66 both when isolated or in the setting of tuberous sclerosis, and for hamartomas in other sites and settings. 87-70

Given these above characteristics, these tumors indeed fulfill the criteria for, and are best described as, glial hamartomas. 8, 19, 20, 24, 53, 71

Since mitoses, by definition, are very rare, if at all present in these lesions, no clinically significant benefit should be expected from anti-mitotic ionizing radiation beyond that expected from background spontaneous regression as part of the natural evolution of these tumors. 9, 10, 13, 14, 16

Due to the severe adverse effects, moreover, of radiation on incompletely myelinated and still developing brain—including severe mental and growth retardation, psychiatric problems, vascular occlusions and the induction of second tumors—attempts at treatment via ionizing radiation are now universally contraindicated in young children.

For similar reasons, anti-mitotic chemotherapy can also offer no benefits. In previous studies reporting minor treatment effects, investigators failed to stratify results for those with “low-grade gliomas (LGG)” or “optic pathway gliomas (OPG)” into those with Grade I pilocytic gliomas versus those with Grade II fibrillary astrocytomas. As with initial reports ascribing benefits to radiation therapy, these studies also did not factor for the fact of spontaneous regression acknowledged by their authors 31, 53, 72 and often include instances of tumor regression long after the cessation of therapy as a treatment effect. 73 Whenever recurrences and regressions do occur, again, they often violate the timeframes set by Collins’ law for neoplastic growth. 12, 48

Declining acuity has long been well-known and documented not to correlate with tumor size or with tumor enlargement. 9, 35, 74, 75, 76, 77 Even the spontaneous regression of tumors can reduce visual acuity and function by distorting nerve axons. 31, 74 For reasons unjustified, a loss of vision is nonetheless used in many treatment protocols as a triggering measure to initiate chemotherapy, or, in older children, radiotherapy. 7, 77, 78

Ignoring the fact that even a spontaneously shrinking tumor intrinsic to the visual pathways can reduce visual acuity, it should be of no surprise then if subsequent immediate radiographic evidence demonstrates a reduction in tumor size, with the temporal correlation held to support an effect of the “treatment,” rather than a process already in play. 74

More recent surveys and other studies, particularly from the neurosurgical literature, with some specifically addressing in part some of these concerns have confirmed the lack of beneficial treatment effects in the face of demonstrated toxicities. 12,17,18

Optic nerve gliomas situated anterior to the chiasm may appear as threatening to involve this structure and affect contralateral vision. 31 Despite radiological appearances, such reports are rare 79, 80 and evidence is lacking to show such evolution often occurs 77, 79, 80 or that surgical excision of such tumors 81 would prevent anticipated contralateral eye involvement; one may instead be witnessing instead multicentric nests of cells within different phases of growth rather than a true progression and invasion of cells moving forward. 26, 82

Multifocal growth, as well as regression, may occur contemporaneously or at different times with either or both optic nerves affected, sparing chiasm, or vice-versa. 31, 82 Hence surgical resection of a distal optic nerve tumor may not necessarily prevent later growth more proximally.

Resection of the intracranial portion of an optic nerve near the chiasm, furthermore, can endanger chiasmal blood supply, with spreading necrosis. However, surgical decompression of an expanded nerve sheath, with aspiration of perineural mucoid contents can be considered if visual obstructions are due to mucoid accumulation and hydration. If disfiguring proptosis is present and there is evidence of steady tumoral enlargement on sequential MRI scans, with total absence of the intraocular nerve fiber layer, it is certainly reasonable to surgically remove the intraorbital portion of the nerve, preserving posterior ciliary blood supply and globe for cosmetic purposes. 24, 21, 84, 85

Though some have believed that gliomas occurring in the presence of NF1 have a better visual prognosis compared to those occurring sporadically, such impressions are due to selection biases; since most NF1-associated gliomas are detected by surveillance MRI scans ordered for asymptomatic NF1 patients, many clinically insignificant tumors are thus detected. Individuals without NF1, on the other hand, present to the physician only when they have large, symptomatic masses. Overall survival for those with NF1-associated gliomas, moreover, is worse; since these patients have an underlying mutation in the NF3 tumor suppressor gene, they tend to develop, for reasons not well understood, 86 other, non-neural crest derived, tumors, particularly soft-tissue sarcomas, 32, 82, 87 and myelogenous disorders.

With a lack of beneficial radiative or antimitotic chemotherapeutic effects, and with limited indications for surgical intervention of optic gliomas, the emphasis of management for the moment must therefore be conservative. A reasonable approach is to follow clinical symptomatology, addressing secondary issues as they may arise, i.e., placing a shunt to deal with an obstructive
hydrocephalus, addressing endocrine abnormalities associated with a hypothalamic/chiasmal gliomas, or instituting penalization therapy if a strabismus is present. In rare settings where exophytic growth is noted, when draining symptomatic cysts or mucinoid accumulations may be possible, or whenever there is no hope for visual recovery due to total absence of intraocular nerve fiber layer, excisional surgery can be considered. A comprehensive discussion should take place with the family to ensure their understanding of the lack of efficacy of anti-mitotic regimens and of the not-inconsequential adverse effects they induce. It follows that frequent neuroimaging in those known to harbor a tumor may not be warranted. Use of the more precise term “hamartoma,” rather than the broader designation of “tumor,” which is psychologically more threatening and evocative of neoplasms, can be helpful. 8, 71 In children who also have NF1, pointing out the melanocytic hamartoma Sakurai-Lisch nodules that grow post-natally on the irides can serve as a helpful educational analogy. More often than not, parents are relieved to hear that their child may not need as many repeated examinations, including MRIs under sedation, and that they need not agree to some recommendations for current antimitotic treatments that, even by reports of their proponents, provide mediocre results with non-negligible adverse effects, in order to be considered responsible parents. Despite the relatively decreased cavitary space available for the expansion of intracranial masses, until efficacious treatment modalities become available, glial hamartomas which occur either intracranially or intraorbitally should be approached in much the same conservative way that ophthalmologists have to date managed those which occur intraocularly. 8, 24, 71, 82

Indeed, to imply that patients with such bona fide tumors, enlarging or otherwise, could benefit from antimitotic treatments, such as radiation or current genotoxic chemotherapy, as a means to avoid “ nihilistic” attitudes towards disease is akin to proposing such therapies to thwart the sometimes undesirable growth of retinal and optic disk hamartomas, 80, 81 or of limbal dermoids. In face of our current-day knowledge, persisting on applying such antimitotic and genotoxic regimens for tumors such as juvenile pilocytic astrocytomas that more specifically are hamartomas, like so many other so-called “controversies,” would represent an example of faith-based, rather than evidence-based, medicine. As is often the case, the physician’s dictum first to do no harm comes to mind. With genotoxic properties and systemic diffusion, antimitotic chemotherapy now being promoted may be predicted to cause secondary tumors, 80 developing elsewhere within the body and become increasingly evident many years following treatment. 81, 82 as for radiation therapy by now already well-established. Such effects would be even more likely in patients treated at a young age, and in those already harboring germline mutations in tumor suppressor genes such as for neurofibromatosis or tuberous sclerosis.

It will be very useful to stratify and separate the radiologically-defined behavior of Grade I juvenile pilocytic astrocytoma hamartomas from Grade II astrocytoma neoplasms in ongoing studies of antimitotic chemotherapeutic regimens. If the non-stratified radiologic data can ultimately be stratified and published, current multicenter trials using anti-mitotic regimens ineffective against such optic glioma hamartomas which, by definition have little to no mitoses, could be put to good use and serve as effective surrogates to delineate the natural history of these tumors. These studies could then be used in a most constructive manner to determine the effectiveness of novel and more appropriately targeted non-antimitotic treatments such as, for example, ripamycin for inhibition of mTOR, or bevacizumab to inhibit angiogenesis, 73, 93, 94 and for other yet untested pharmacologic agents that will offer better potential in years to come.

The use of these and other newer agents in patients with large intraocular hamartomas threatening ocular structures and integrity, 88, 89 can also afford unique opportunities to observe drug effects on these lesions directly, using the eye as a transparent laboratory to investigate treatments more often needed within the orbit and skull. Perhaps such directly observable responses to non-mutagenic pharmacologic agents may help guide us toward more efficacious therapies for juvenile pilocytic astrocytoma optic pathway gliomas.

CME ANSWERS
1. No. The terminology “optic pathway gliomas” and “low-grade gliomas” is also inclusive WHO Grade II astrocytomas.
2. No. Hamartomas may grow in self-limited form during the period of development.
3. No. A decline in visual acuity indicates a distortion of axons which may also occur during tumor shrinkage.

REFERENCES


OPTIC PATHWAY GLIOMAS ARE NEOPLASMS!

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LEARNING OBJECTIVES
Understand the differences and similarities between hamartomas and neoplasms, and that optic pathway gliomas are neoplasms.

CME QUESTIONS: TRUE/FALSE
1. Hamartomas do not in general cause symptoms
2. Spontaneous regression does not occur with neoplasms.
3. There is no proof of the efficacy of chemotherapies in optic pathway gliomas

KEYWORDS
1. Optic Pathway Glioma
2. Neoplasm
3. Hamartoma

INTRODUCTION
Hoyt and Bagdassarian\(^1\) popularized the notion that optic pathway gliomas are hamartomas. Parsa has continued to argue extensively that optic pathway gliomas are congenital developmental lesions, not neoplastic, and therefore should not be treated, even when there is evidence of clinical or radiographic progression.\(^2\)\(^-\)\(^4\)

However, more recently MRI techniques have provided clinicians a more detailed method for observing the natural history of optic pathway gliomas not available decades ago. Now most clinicians today dealing with optic pathway gliomas have realized that the growth patterns are varied and unpredictable.\(^5\) While most optic pathway gliomas are benign, some clearly act aggressively.\(^6\)

The question boils down to this: are optic pathway gliomas hamartomas or slowly-growing neoplasms? It is our opinion that optic pathway gliomas are slowly-growing neoplasms and not hamartomas

OPTIC PATHWAY GLIOMAS DO NOT SATISFY THE DEFINITION OF HAMARTOMAS.
A hamartoma is a "benign, focal malformation that resembles a neoplasm in the tissue of its origin . . . it grows at the same rate as the surrounding tissues. It is composed of tissue elements normally found at that site, but which are growing in a disorganized mass. They occur in many different parts of the body and are most often asymptomatic and undetected unless seen on an image taken for another reason."\(^7\)

Opitz and Jorde\(^8\) wrote, “hamartomata are localized overgrowths of a single tissue or combination of tissues, indigenous to the affected body part or organ, usually growing at the same rate as the normal components and causing little pain or functional impairment.”

Optic gliomas on the other hand:
1. Can demonstrate growth at rates more rapid than that of the visual pathways or brain.
2. Can destroy the structures within and around which they are growing.
3. Are often symptomatic. While many are asymptomatic, up to 50% of patients with neurofibromatosis type 1 and optic gliomas exhibit vision loss to some degree.\(^9\) Hypothalamic gliomas can cause diencephalic syndrome and obstructive hydrocephalus.
4. Can metastasize in the absence of shunt manipulation,\(^10\) a behavior not characteristic of hamartomas.

HISTOPATHOLOGICALLY, OPTIC PATHWAY GLIOMAS ARE NEOPLASMS
1. Many are grade I juvenile pilocytic astrocytomas, just like the childhood cerebellar juvenile pilocytic astrocytomas, which are not hamartomas because they do not look at all like normal cerebellum as a hamartoma would.
2. Some optic pathway gliomas are grade II fibrillary astrocytomas, and it is artificial to separate those which might be predominantly grade I from those with grade II components, because many are not biopsied (due to the risk associated with biopsy) and sampling error may occur.
3. The fact that they, like subependymal giant cell tumors and craniopharyngiomas, do not generally undergo malignant transformation does not put them into the hamartoma category.
4. As Wahrath et al.⁶ and Miller¹¹ have discussed, some optic pathway gliomas may exhibit markers of cellular proliferation identified by using MIB-1, an antibody to the Ki-67 antigen,¹² and AgNOR (silver nuclear organizing region)¹³ techniques. Like pilocytic astrocytomas in other brain locations,¹⁴-¹⁶ a portion of optic pathway gliomas have elevated proliferative activity (MIB-1 labeling index of 2-3%),¹² and this is associated with more aggressive tumor behavior.¹²,¹⁶

THUS, OPTIC PATHWAY GLIOMAS SATISFY THE DEFINITION OF NEOPLASMS
A neoplasm is defined as an “abnormal mass of tissue as a result of . . . and abnormal proliferation of cells. The growth of neoplastic cells exceeds and is not coordinated with that of the normal tissue around it. . . . It usually causes a lump or tumor.”¹⁷ The growth characteristics and pathology of optic pathway gliomas would be more consistent with a neoplasm.

SPONTANEOUS IMPROVEMENT AND RESOLUTION CAN BE SEEN IN NEOPLASMS
This behavior is not a characteristic of just hamartomas as it occurs in some neoplasms as well. For instance, neuroblastomas, the majority of which are neoplasms, may also demonstrate spontaneous regression. In one study,²² of 53 of six month old infants found to have neuroblastoma on screening, 17 (32%) exhibited complete spontaneous regression. In addition, cases of stage IV neuroblastoma, with metastases, later demonstrating spontaneous regression, have been observed.

THERE IS PROOF THAT ANTI-MITOTIC THERAPIES ARE EFFECTIVE IN OPTIC PATHWAY GLIOMAS
Chemotherapy is used when radiographic and/or clinical progression are documented.

Using radiologic data primarily as the outcome measure, the combination of carmustin and vincristine, the most common regimen, was associated with a 3 year progression-free survival rate of 77%²⁰ and 5 year progression-free survival rate of 69% in patients with NF1.²⁰ Although allergies may occur, this regimen in general is very well tolerated in children.

Data regarding visual outcomes following chemotherapy for optic pathway glioma now exist. In our retrospective multi-center review of 115 patients treated with chemotherapy over a ten year period at ten sites throughout the world, at the completion of therapy, visual acuity improved (32% of subjects), remained stable (40%), or declined (28%).³¹ This rate of improvement (32%) can not be explained by the occasional phenomena of spontaneous regression.²²,²³

Radiation therapy, again using radiologic data, has been shown to be efficacious for optic pathway gliomas with reported 10 year progression-free survival (PFS) rates of 66-90%.²⁴,²⁵ However, radiation is no longer used first-line because of the risk of cognitive decline, endocrinopathies, cerebrovascular disease, and secondary malignancies.⁵

Newer therapies are being explored.⁵ Our developing understanding of the biology of these tumors carries the promise of improved outcomes for this tumor. Inhibitors of BRAF, MEK and mTOR are already in clinical trials. In addition, drugs targeting tumor angiogenesis, such as bevacuzimab, have been shown to yield objective responses in recurrent/refractory optic pathway gliomas²⁹ and are being evaluated in larger studies.

IMPLICATION OF DESIGNATING OPTIC PATHWAY GLIOMAS AS HAMARTOMAS
It is a disservice to and potentially dangerous for patients with optic pathway gliomas and their families to call these lesions hamartomas not requiring treatment.²,³ Families may get the false impression that if treatments are ineffective or unnecessary, clinical follow-up and imaging are also unnecessary.

CONCLUSION
In summary, based upon their growth patterns and histopathology, optic pathway gliomas are not hamartomas but truly are neoplasms. Spontaneous regression can be seen in neoplasms. Chemotherapies should be used when radiographic or clinical progression occurs. Other more directed therapies will certainly be used in the future.

APPENDIX
Choristomas, “forms of heterotopia, are closely related benign tumors. These tumors also contain normal tissues but are found in abnormal locations.”⁷

CME ANSWERS
1. true
2. false
3. false

REFERENCES


