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Neuro-ophthalmology Update

Intracranial pressure and skull remodeling

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Abstract

In this article we review bony changes resulting from alterations in intracranial pressure (ICP) and the implications for ophthalmologists and the patients for whom we care. Before addressing ophthalmic implications, we will begin with a brief overview of bone remodeling. Bony changes seen with chronic intracranial hypotension and hypertension will be discussed. The primary objective of this review was to bring attention to bony changes seen with chronic intracranial hypotension. Intracranial hypotension skull remodeling can result in enophthalmos. In advanced disease enophthalmos develops to a degree that is truly disfiguring. The most common finding for which subjects are referred is ocular surface disease, related to loss of contact between the eyelids and the cornea. Other abnormalities seen include abnormal ocular motility and optic atrophy. Recognition of such changes is important to allow for diagnosis and treatment prior to advanced clinical deterioration. Routine radiographic assessment of bony changes may allow for the identification of patient with abnormal ICP prior to the development of clinically significant disease.

Keywords: Intracranial pressure, Hypotension, Hypertension, Bony changes

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Introduction

In this article we review bony changes resulting from alterations in intracranial pressure (ICP) and the implications for ophthalmologists. Before addressing ophthalmic implications, we will begin with a brief overview of bone remodeling. Two specific situations will then be addressed: (1) ophthalmic implications of bony changes seen with intracranial hypotension and (2) ophthalmic implications of bony changes seen with intracranial hypertension.

Dynamic bone

The maintenance of bone involves a dynamic process mediated by continual absorption by osteoclasts and creation of new bone by osteoblasts. (1) The balance of bone absorption and formation is mediated in part by mechanical loading or stress on the bone. The strain-sensitive cells are thought to be osteocytes. While this process is more active during childhood, even mature bone has the potential of remodeling. This can be loosely classified into three categories: (1) primary disease, (2) hormonally regulated changes in bone, and (3) alteration in stress or loading pressure. We are all familiar with more common primary diseases of bone, such as fibrous dysplasia, Paget's disease, and osteogenesis imperfect. With the exception of trauma, osteoporosis is the most common abnormality of bone. The cause of osteoporosis is multifactorial and likely is in part connected to age related hormonal changes (i.e. menopause). These examples only serve to illustrate the plasticity of bone.

We will now focus on the reshaping of bones in response to mechanical forces. Bony changes in response to alterations in ICP fall in this group. We are all familiar with bone

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remodeling in response to tumors. Bone may be infiltrated or destroyed by malignant neoplasm. Changes in bone due to malignant tumor infiltration are more complex than simple changes in mechanical loading. However, bony changes in response to benign neoplastic disease, molding and thinning of adjacent bone, are likely pressure related. Fig. 1 illustrates bony remodeling secondary to long standing pressure exerted by an expanding benign hemangioma. The loss of stress of daily activity (loss of loading) with simple disuse results in bony changes. For example, prolonged bed-rest has been shown to result in bone remodeling with a reduction in density.[2] In addition, previous work has shown that during prolonged bed rest, the skull will increase in mass, which is believed to result from a net bone formation from the increased ICP from a chronic rostral shift in fluid.[1] Astronauts experience a similar effect with extended periods of zero-gravity.[3–5] Long bones may resorb due to the lack of mechanical loading required to maintain bone density. Before specifically addressing the bony effects of altered ICP, we should focus on two related entities: silent sinus syndrome and pneumosinus dilatans.

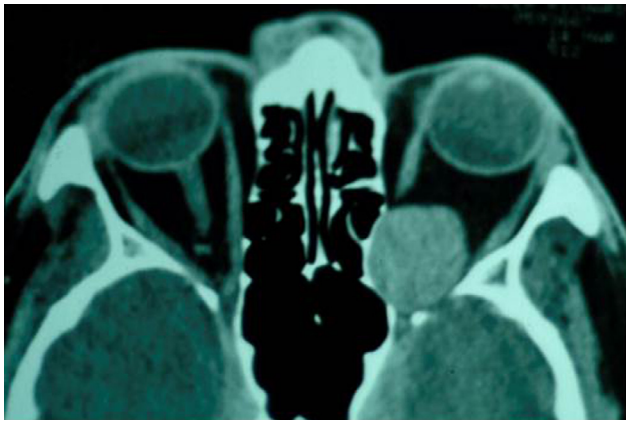

Figure 1. Axial computed tomography demonstrating bony remodeling secondary to a slowly enlarging benign orbital neoplasm.

Silent sinus syndrome

''Silent sinus syndrome'', first described in 1994 by Soparkar et al.[6] is characterized by spontaneous maxillary sinus atelectasis with orbital floor resorption, resulting in ipsilateral enophthalmos and hypoglobus (Fig. 2). Due to an absence of sinus disease symptoms, globe displacement is frequently the presenting sign, hence the name ''silent'' sinus syndrome. In rare cases ocular motility may also be affected.[7–9] Although patients of all ages can be affected, onset has been most commonly reported to occur in the fourth decade of life.[1,10–15] The mechanism of atelectasis in silent sinus syndrome has been postulated to be negative sinus pressure created by prolonged sinus hypoventilation due to outflow obstruction, and/or chronic inflammation with contraction of fibrous bands, resulting in distortion of the antral wall. Additionally, bone resorption occurs, further contributing to orbital floor displacement and altered globe position. The initial cause of outflow obstruction is not always clear; however, numerous etiologies have been implicated including a mucocele or polyp, lateralized middle turbinate, inspissated mucus, and intra-orbital ethmoidal (Haller) cells.[16,17] Although silent sinus syndrome has no direct relationship with ICP, it is relevant because the mechanism of an alteration in pressure gradient affecting an orbital wall with resulting enophthalmos is analogous to the process and consequences seen with intracranial hypotension.

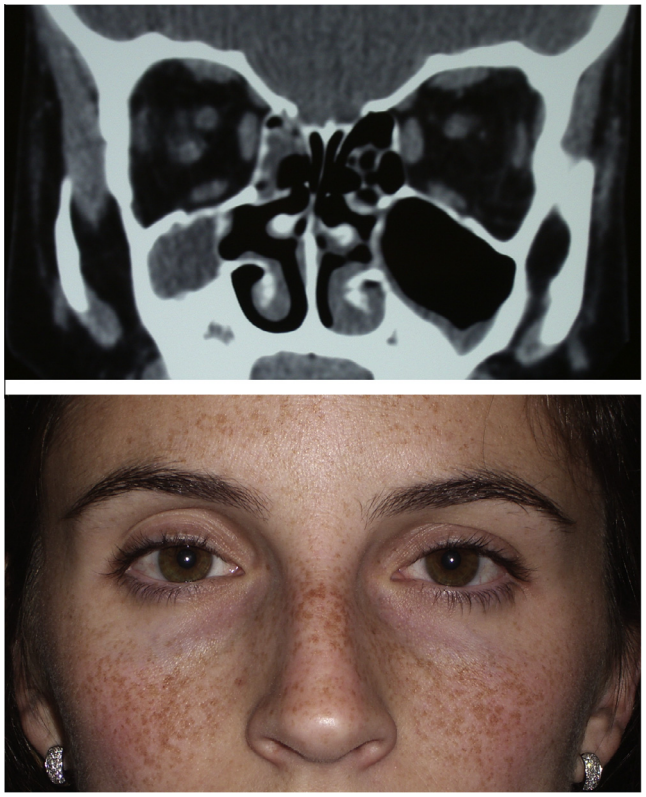

Figure 2. Silent sinus syndrome. Atelectasis of the maxillary sinus (top) results in downward bowing of the orbital floor resulting in enophthalmos (bottom).

Pneumosinus dilatans

Pneumosinus dilatans is a somewhat uncommonly used term that describes enlargement of the paranasal air sinuses. Sinus expansion has been described to occur without an identifiable cause, or in association with other abnormalities including fibro-osseous disease and meningiomas.[18,19] Presenting symptoms have included headache and ocular misalignment. Decreased visual acuity and field loss have been attributed to presumed optic nerve compression by an enlarged sphenoid sinus.[20] Many patients have been described as presenting with proptosis, whereas in others no mention of globe position was provided.[18–21] Of particular interest, in 1992 Schayck and Niedeggen described two patients with cerebral hemiatrophy who developed enlargement of the sphenoid, ethmoid and frontal sinuses.[21] They termed this pneumosinus dilatans, but noted that sinus enlargement occurred after cerebrospinal fluid (CSF) shunting. It seems likely that these cases represented intracranial hypotension related bone remodeling. Perhaps other cases labeled as pneumosinus dilatans also occurred secondary to unrecognized intracranial hypotension.

Intracranial hypotension

Intracranial hypotension related skull remodeling (IHSR) is a fairly recently recognized consequence of abnormally low ICP.[22–26] In patients that have undergone CSF shunting, most often ventriculoperitoneal shunting (VPS), over-shunting can result in bone remodeling, including the bones that make up the orbit. Expanded orbital volume can result in clinically troublesome enophthalmos. The clinical consequences of IHSR are significant. When associated with enophthalmos, we have applied the term ''Sunken eyes, sagging brain syndrome''.[24] This can be of significant cosmetic detriment (Fig. 1). With advanced disease, the enophthalmos becomes so severe that the eyes may actually lose contact with the eyelids with resultant severe ocular surface disease. A pocket of air forms in the space between the eyelid and the globe beneath the superior orbital rim, such that with supraduction, the cornea completely loses contact with the eyelid (Fig. 1). Several other findings are worthy of mention. First, many patients develop significant ocular motility problems, in particular a marked reduction in supraduction. Abnormal vertical ductions can be explained by the mechanical effect of the superior bowing of the orbital roof and displacement of the superior recti muscles. This is analogous to the alteration in vertical ductions seen in patients with the inferior rectus muscle displacement through a comminuted orbital floor fracture.[27] Malposition of the globe or muscles may adversely affect the vector with which the recti muscles relate to the globe. Abnormal horizontal ductions are more difficult to explain and may relate to shortening of the muscles with loss of optimal sarcomere filament overlap. Other possible mechanisms include neurologic from cranial nerve or brainstem pathology. A number of patients also develop an optic neuropathy. This likely relates to bony changes at the level of the orbit apex resulting in malformation of the optic canals.[25] Another possibility is that intracranial hypotension causes stretch injury from displacement of the chiasm.

Our understanding of this syndrome (IHSR) is evolving. In 1996, Meyer et al. identified a novel syndrome producing bilateral enophthalmos.[26] The report described three patients with congenital hydrocephalus who developed bilateral enophthalmos following ventriculoperitoneal shunting (VPS). This was followed a decade later by two reports of similar patients.[22,23] At that time proposed mechanisms included fat atrophy and expansion of the bony orbit.[22,23,25] In our manuscripts titled ''Sunken eyes, sagging brain syndrome: bilateral enophthalmos from chronic intracranial hypotension'', published in 2011, we identified that skull remodeling occurred secondarily to chronic intracranial hypotention, in four patients who developed enophthalmos following VPS.[24] Shunting of CSF is a well-established treatment for increased ICP and over-shunting is a known complication. In pediatric patients, when the skull is still developing over-shunting can lead to premature suture fusion and secondary craniosynostoses, inhibiting normal expansion of the cranial vault.[28,29] IHSR represents an additional bony consequence of intracranial hypotension. The initial case descriptions illustrate that it may affect children and adults. With chronic intracranial hypotension, the pressure gradient across the bone of the orbital roof is altered from decreased force from the intracranial side. This effect theoretically causes not only a net resorption of bone because of decreased stress but an effective intracranially-directed force across the roof causing orbital expansion. The process occurs progressively over months and can be clinically apparent in as little as 18 months after shunt placement.[25]

The condition that best parallels sagging brain, sunken eyes syndrome is the ''silent sinus syndrome''. Previous reports on ''silent sinus syndrome'' identified an altered pressure gradient across the bone of the orbital floor from a decrease in the intramaxillary sinus pressure, just as described for the orbital roof from a decrease in ICP in our patients. In addition, demineralization of the orbital floor consistent with bony remodeling has been identified in ''silent sinus syndrome.''[30] This is consistent with our proposed mechanism for bony changes resulting from IHSR.

Although IHSR appears to be the major contributor to enophthalmos, other factors also contribute; following correction of intracranial hypotension, a small but rapid improvement in enophthalmos is seen within days. This suggests that additional factors, other than bone remodeling, are involved. First, forward movement of the globe after shunt revision may result from increased hydraulic force generated by the increased CSF pressure in the subarachnoid space of the optic nerve just as raised pressures can flatten the globe in cases of intracranial hypertension. Second, a rise in ICP causes an elevation in venous pressure within the cavernous sinus and thus the orbital venous pressure, which would cause increased orbital soft tissue blood volume. Finally, the cuff of CSF around the optic nerve would also expand with normalization of the ICP. Assuming a cylindrical optic nerve with a diameter of 5 mm and an intraorbital optic nerve length of 25 mm, the added volume would be on the order of 0.86 cm^3.[24]

IHSR also affects other bony structures. We have observed marked sinus enlargement in patients IHSR.[25] This is apparent in the patient illustrated in Fig. 1. Thus far patients have been identified on the basis of enophthalmos. This is reflective of our practices focusing primarily on ophthalmic disease. Sagging brain, sunken eyes syndrome may represent only a subset of patients with IHSR. Some IHSR patients may not have enophthalmos or could develop enophthalmos late in the disease. For this reason, we use the ''intracranial hypotension related skull remodeling'' more generically and reserve ''sagging brain, sunken eyes syndrome'' for those that develop clinically significant enophthalmos.

Radiographic changes in the sphenoid sinus may provide be a means of diagnosing patients with IHSR. Ideally, we would like to be able to identify patients prior to the development of enophthalmos. In advanced disease marked enlargement of the sphenoid sinus is easily appreciated (Fig. 3). We have used the terms ''bubbling'' or ''bubble sign'' to describe lateral extension of the sphenoid sinus (Fig. 4, top). Normally the sphenoid sinus does not extend much further laterally than the orbital apices. With ''bubbling'' the sphenoid sinus is seen to extend far lateral to the posterior orbit. Bubbling is most visible on axial computed tomography inferior to the orbital apices. Another radiographic finding worth noting is aeration of the anterior clinoids: the enlarged sphenoid sinus is seen to extend into the anterior clinoids (Fig. 4, bottom). Sphenoid bubbling and acquired aeration of the clinoids are useful only in identifying advanced stages of IHSR.

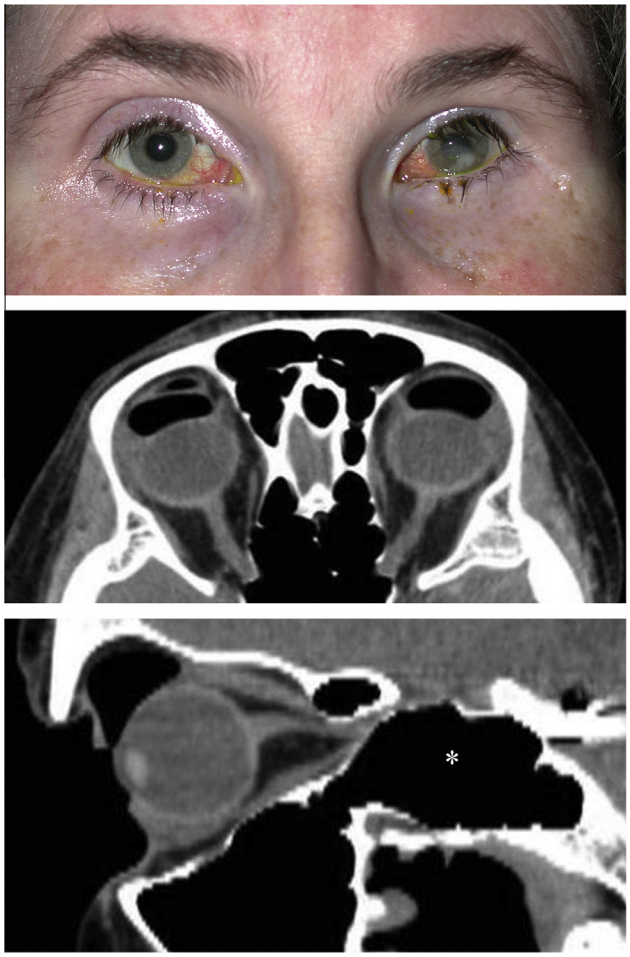

Figure 3. Intracranial hypotension related skull remodeling with enophthalmos (sunken eyes, sagging brain syndrome). Ocular surface exposure results from loss of contact between the globes and eyelids (top). Note the pockets of air beneath the superior orbital rim, under the eyelid in which the cornea sits with supraduction (middle and bottom). The asterisk (*) marks the sphenoid sinus which is also markedly expanded.

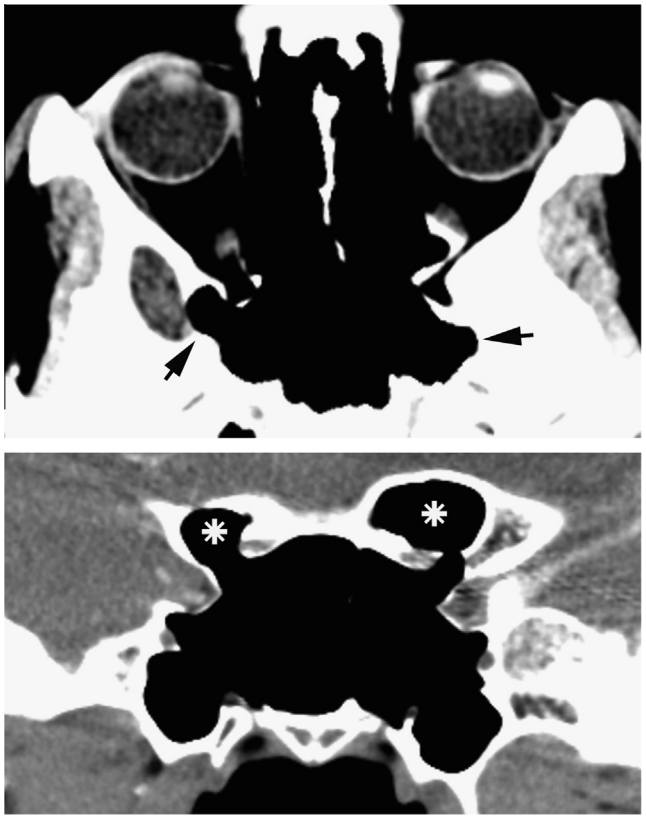

Figure 4. Axial computed tomography (top). Sphenoid ''bubble sign'', occurring with expansion of the sphenoid sinus with chronic intracranial hypotension. The sphenoid sinus is seen to extend far lateral to the posterior orbit (arrows). Coronal computed tomography (bottom). Aeration of the anterior clinoids occurring with chronic intracranial hypotension. The enlarged sphenoid sinus has extended into the anterior clinoids (*). Sphenoid bubbling clinoid aeration are indicative of advanced intracranial hypotension related skull remodeling.

Markedly abnormal sphenoid sinus size may not be encountered before clinically relevant enophthalmos has appeared. In such cases, the sphenoid sinus may enlarge, but not more than that encountered in the normal population. A more sensitive tool than absolute size is a change in the size of the sphenoid sinus. In patients with VPS, routine documentation of sphenoid sinus dimensions would likely identify patients before the development of clinically significant enophthalmos. A larger group of patients with VPS will need to be observed to precisely determine how often and at what stage of disease changes in the sphenoid are encountered.

When possible, initial management of sagging brain, sunken eyes syndrome should include correcting the intracranial hypotension.[24] ICP normalization will likely halt disease progression and as discussed above some patients may experience a small immediate reduction of enophthalmos. Whether resolution of the intracranial hypotension will result in correction of the bony expansion remains unknown. In a series of 23 patients with silent sinus syndrome, following re-establishing aeration of the sinus, 22 patients had partial or complete normalization of globe position.[31] Therefore, observation should be considered following normalization of ICP prior to proceeding with surgical augmentation. When medically necessary or when improvement is not seen following normalization of ICP, surgical intervention may be considered. Volume augmentation has been reported. Both orbital floor and roof implants have been described.[22,23,26] Given that the abnormality lies primarily with the orbital roof, it is not surprising that better results have been reported with roof implants.[22,23] With floor implants unwanted superior displacement of the globe occurred. In patients who decline shunt revision as well as placement of an orbital implant, a tarsorrhaphy may be beneficial. Most patients would consider this procedure cosmetically inferior to shunt revision and orbital volume augmentation and it should probably be viewed as a ''last resort''.

Intracranial hypertension

With such robust skeletal changes being seen with intracranial hypotension, one logically might question whether there is a converse effect from intracranial hypertension. Although no changes with any symptomatic affect have been identified, radiographic changes with diagnostic implications have been recognized. The term ''empty sella'' has long been used to describe the radiographic appearance of the sella turcica, when not filled by the pituitary gland (Fig. 5).[32] This has been assumed to be due to flattening of the pituitary

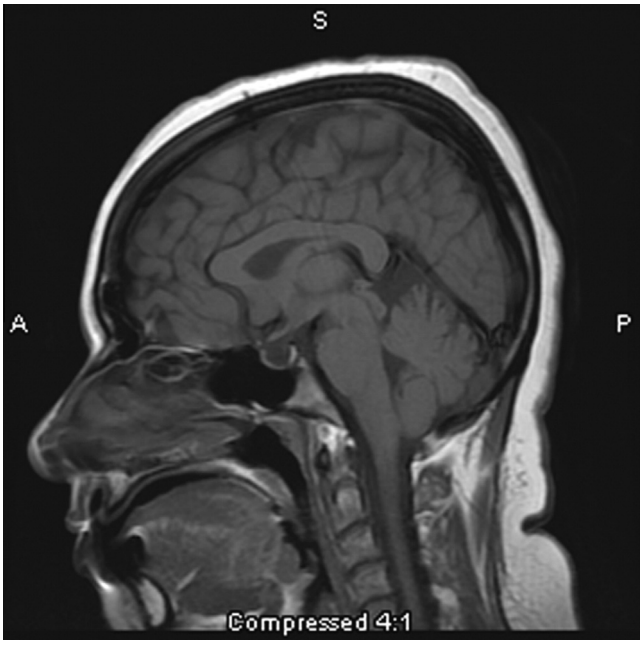

Figure 5. Sagittal MRI demonstrating an ''empty sella''. A large sella without readily apparent pituitary tissue is a common finding indicative of elevated intracranial pressure. (Image courtesy of Neil Miller).

gland against the base of the sella turcica. More recently investigators have suggested that this is at least in part due to the enlargement of the bony cavity. In 2013 Ranganathan and colleagues, using MRI to assess the bony cavity and volume of the pituitary gland, found that the sella was significantly larger in patients with elevated ICP than controls.[33] In a similar study published in 2014, Kyung, Botelho and Horton reported that ''The cross-sectional area of the sella was 38% greater in the patients with pseudotumor cerebri, with only a slight reduction in mean pituitary gland size.''[34] Presumably other bony changes occur along with enlargement of the sella turcica. The clinical or diagnostic significance of such changes remains to be determined.

Closing comments

The clinical consequences of IHSR with enophthalmos are potentially devastating. The effect of even mild enophthalmos can be easily appreciated. In advanced disease enophthalmos develops to a degree that is truly disfiguring. The most common finding for which subjects are referred is ocular surface disease, due to loss of contract between the eyelids and the cornea. Other findings include abnormal ocular motility and optic atrophy. Recognition of such changes is important to allow for diagnosis and treatment prior to advanced clinical deterioration. Routine radiographic assessment of bony changes may allow for identification of patients with abnormal ICP prior to the development of clinically significant disease.

Conflict of interest

The authors declared that there is no conflict of interest.

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