Intracranial hypertension associated with obstructive sleep apnea: A discussion of potential etiologic factors ☆

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ABSTRACT

Obstructive sleep apnea has been shown to increase intracranial pressure, and to be a secondary cause of intracranial hypertension. There are a few theories that attempt to explain this relationship, however there is little data, and even less recognition among physicians that this actually occurs. This paper discusses multiple pieces of data, from anatomical correlates to biochemical information involving neuro-excitotoxicity, as well as hematologic factors and issues surrounding brain edema and blood–brain barrier dysfunction. A complex paradigm for how obstructive sleep apnea may lead to increased intracranial pressure is thus proposed. In addition, suggestions are made for how obstructive sleep apnea must as a result be managed differently in the setting of idiopathic intracranial hypertension.

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Introduction

Intracranial hypertension can be idiopathic, or it may be identified to be due to a specific cause. Secondary etiologies of intracranial hypertension may include cerebral venous abnormalities, medications such as tetracyclines and retinoids, some endocrine disorders, obstructive sleep apnea and renal failure [1]. Idiopathic intracranial hypertension (IIH) is classically defined using the modified Dandy Criteria. They are: (1) signs and symptoms of increased intracranial pressure; (2) no localizing signs except abducens nerve palsy; (3) CSF opening pressure $\geqslant 25$ cm H_2O with normal CSF composition; and (4) normal neuroimaging (ruling out venous sinus thrombosis) [2]. This paper will aim to discuss the relationship between intracranial hypertension and obstructive sleep apnea (OSA), with the goal of elucidating potential etiological factors that have heretofore gone unrecognized. The hope is that this will help improve the focus for diagnosis and management of these complicated patients.

Intracranial hypertension in obstructive sleep apnea

There are several mechanisms proposed for how OSA may increase intracranial pressure (ICP). Jennum and Borgesen showed in 1989 that individual apneas may acutely elevate ICP as well as arterial pressure, but also that in patients with OSA more than half of them have elevated ICP while awake in the morning, and the ICP

in the morning is higher than it is in the evening. ICP was higher during REM sleep, when more apneas occur. They discuss how hypercapnia and hypoxia play a role in cerebral vasodilation to effect this increase in ICP via an increase in cerebral blood flow, although they suggest that the increase in arterial pressure and an increase in central venous pressure may also be contributing to the increase in ICP. Increased intrathoracic pressure at the termination of the apnea may also be involved [3]. There has been an association of OSA with IIH (also called pseudotumor cerebri) as well as papilledema; in some cases these will resolve with treatment of the OSA [2,4–7]. There is an hypothesis that central obesity (known to be present in many cases of OSA and IIH) raises intra-abdominal pressure which leads to poor venous return from the brain via an increase in pleural and cardiac filling pressures. This poor venous return would lead to increased ICP [8]. In the presence of IIH, it should be considered that even mild OSA with minimal hypoventilation might lead to a clinically significant rise in cerebral blood flow, and thus in intracranial pressure.

Anatomical factors

Alperin et al. demonstrated that in IIH (in obese women) what is seen is decreased jugular venous drainage and evidence of increased interstitial fluid volume in gray matter [9]. It has been noted that there can be a collapsible segment in the venous outflow tract from the skull (transverse sinus) in patients with IIH, and that this can account for elevated ICP in IIH [10]. IIH has been demonstrated to be caused in some people by internal jugular venous compression in part by an elongated styloid process [11]. Regarding obstructive sleep apnea, it is well known that fat depo-

sition may compress upper airway structures contributing to OSA in those who are obese and lead to narrowing of the upper airway [12]. What does not seem to have been discussed in the literature, or investigated, is whether obesity may lead not only to compression of the airway but also to a propensity for jugular venous collapsibility or narrowing due to fat deposition in the neck, and in this fashion contribute to increased ICP and IIH, via increased resistance in the jugular veins. This explanation might account for the relationship of obesity to IIH, and might be an important etiologic factor to consider in the pathogenesis of IIH. However, while obesity is associated with IIH, it is not one of the modified Dandy criteria [2] and there are many thin people with IIH. This suggests that there may be other factors contributing to poor jugular venous drainage that are independent of obesity. It is known that obstruction of the nose, causing mouth breathing, may lead to developmental changes in the maxilla and mandible that include retraction of the mandible. The jaws end up growing vertically rather than forwards in the face, which narrows the bony airway [13]. This would obviously increase the risk of OSA, however if the mandible is retracted and the tongue is more posteriorly placed, this will also occupy space in the neck previously reserved for the internal jugular veins. Therefore, mouth breathing in childhood may not only increase the risk for OSA, but it may also raise the risk for increased resistance in the jugular veins and IIH. While OSA may be causative for IIH by the mechanisms stated in the first paragraph above, it may be also true that OSA and IIH go hand in hand because they are contributed to by the same developmental and acquired anatomical factors as dictated by mandible and tongue position as well as fat content of the neck. These ideas require further investigation. Also, it has been demonstrated in OSA patients that there is a forward head posture that is associated with disease severity; there is evidence that the airway is narrow while OSA patients are awake and that they adopt a compensated head posture as a result [14]. Might this forward head posture also impact upon the jugular veins in some fashion, perhaps at the level of the jugular foramen? Forward head posture has been associated with thoracic outlet syndrome [15], which is in turn known to be capable of compression of the veins of the neck and subclavian fossae [16]. It may be that IIH results when there is a combination of factors that leads to resistance in the jugular veins passing a certain threshold.

Neuro-excitotoxicity

Little known is the fact that in OSA, it has been shown that there is glutamate-induced neuro-excitotoxicity. This has been demonstrated to lead to apoptosis of hippocampal neurons, as induced by apnea [17]. Also less recognized is the finding that glutamate and quinolinate, both neuro-excitotoxins, may lead to brain edema. Both substances stimulate the NMDA (N-methyl-D-aspartate) receptor [18–22]. It is well known that the elevated levels of ammonia seen in fulminant hepatic failure will cause cerebral edema. This has been shown to be due in part to the osmotic effects of glutamine, generated in astrocytes from ammonia and glutamate in a reaction catalyzed by glutamine synthetase. Upon administration of ammonia, a rise in ICP can be prevented with the use of an inhibitor of glutamine synthetase [23]. This is therefore another possible mechanism for the elevation of ICP in OSA; apnea may cause elevation of glutamate which may lead to brain edema, increasing ICP in this way. Even in the absence of OSA, this data indicates that elevations in glutamate and ammonia might cause problems for people with impaired drainage of cerebrospinal fluid (CSF). Alperin et al., mentioned above, provided evidence that there may be brain edema in IIH [9]. Reduction in brain volume after 6 months of CPAP treatment suggests the presence of brain edema in OSA. A recent study in mice indicates that intermittent hypoxia as is seen in OSA, led to higher brain water content in addition to changes in Aquaporin levels [24]. An MRI-DWI study on OSA patients showed increased apparent diffusion coefficients in the hippocampus, amygdala and putamen, suggesting hypoxia and vasogenic edema as a result of the apnea [25]. Therefore, we have evidence of brain edema in both IIH and OSA, and we have a biologically plausible mechanism for how this may be mediated: glutamate neuro-excitotoxicity as seen in OSA. The decrease in jugular venous drainage seen in IIH may be the factor which allows ICP to increase and be sustained in this setting. Further study would be required to confirm these hypotheses.

Glutamate neural damage may be potentiated by hypoglycemia and energy deficiency in the brain. Glucose as an energy source is vital to keep glutamate from accumulating in the brain. Hypoglycemia, hypoxia, and brain hypoperfusion all cause the same pattern of neural damage which is identical to that seen in excitotoxin damage [26]. There is an increased incidence of neurological illnesses which are influenced by neuro-excitotoxins in areas where there has been the condition of famine [26]. This suggests that as OSA and IIH patients attempt to lose weight in order to improve their condition, that hypoglycemia should be carefully avoided to prevent glutamate toxicity and any contribution to brain edema.

A stress response induces the release of large amounts of excitatory amino acids like glutamate and aspartate [27]. A recent study showed that exposure to acute stress in rats increases depolarization evoked release of glutamate. This was reduced by pre-treatment with antidepressants [28]. This implies that any type of stress, physiological (such as suffocation) or emotional, may precipitate brain edema and elevation of ICP in those who are susceptible, via the glutamate mechanism. It also implies that antidepressants may attenuate this trigger. This relationship remains theoretical until human studies are conducted, however this potential role of stress in intracranial hypertension may be important for clinicians to consider in the interim.

CPAP use in OSA with IIH

A related factor is the finding that exposure to electromagnetic fields (EMF) may increase quinolinate in CSF [29]. As above, quinolinate may lead to brain edema. We do know that EMF exposures may act via activation of voltage-gated calcium channels, and that this activation can lead to an increase in nitric oxide. Pathophysiological responses to nitric oxide elevations and therefore from EMF may involve an increase in peroxynitrite production, resulting in an increase in oxidative stress and free radical breakdown products [30]. It is also known that peroxynitrite can trigger an increase in NMDA receptor activity (glutamate action) as well as a breakdown of the blood–brain barrier [31], both of which can lead to brain edema [18,32]. Therefore it is biologically plausible that EMF may lead to brain swelling. There is a great deal of research required to investigate this possible phenomenon, but it is worth pondering. Consequently, if confirmed by future study, it is possible that if a person already has impaired CSF drainage or OSA leading to elevations in ICP via other mechanisms, this effect could become clinically significant. If this is true, then a person with OSA and IIH using a CPAP (continuous positive airway pressure) machine may be affected by the EMF of the machine and wake up feeling not much different than they did under the effects of OSA, prior to using the machine. In addition, a CPAP of 12 has been shown to increase intracranial pressure as well as central venous pressure [33]. There is a case report of a man with intracranial hemorrhage who suffered orbital herniation after coughing while on CPAP. The author's best explanation for this occurrence was that the Valsalva effect of breathing against the CPAP machine led to an

increase in cranial venous pressure which caused an increase in intraocular pressure sufficient to precipitate the exophthalmos [34]. Therefore, CPAP may not be the best treatment modality for a patient with IIH and OSA. Perhaps the effect of CPAP on ICP is not significant unless the patient has intracranial hypertension at baseline. Certainly, as above, exhaling against the high pressure of CPAP can create a Valsalva, which is known to increase ICP [34]. For this reason, it may be appropriate in the setting of IIH, for the use of Bi-level to be standard of care, in order to reduce exhalation pressure. Knowing that venous drainage from the skull is a problem in IIH, then if CPAP truly increases central venous pressure, this may contribute to its inadvisability for patients with IIH. It has been demonstrated that Bi-level positive airway pressure will not increase central venous pressure [35]. Based on all of the above, poor tolerance of CPAP causing daytime fatigue should be a clue to the attending sleep physician that the patient's OSA may be complicated by increased ICP and this might indicate further diagnostic evaluation.

Because of the knowledge that IIH patients may be more sensitive to the effects of hypoventilation and of the Valsalva effect on ICP, as described above, this may indicate that IIH patients ought to be managed quite differently regarding any Sleep Medicine evaluation. To minimize the effect of sleep disordered breathing on intracranial pressure, IIH patients may need to be treated under the same criteria we use for children; diagnosis of OSA for an AHI > 1, and titration to an AHI < 1 (AHI = apnea hypopnea index). Given the significance of the human airway problem as detailed by Davidson [36], it may be that all IIH patients should be screened for sleep disordered breathing with a sleep study using the most sensitive instruments and hypopnea criteria.

Disruption of the blood–brain barrier

The above discussion on neuro-excitotoxicity was regarding excitotoxins that are generated in the brain. Ingested glutamate has been thought to be less significant in the presence of an intact blood–brain barrier (BBB), however if there is a breakdown of the BBB, ingested glutamate might have a much greater effect on humans [26], and per the above, even more so in people with IIH. Other excitotoxins, aspartate and cysteine would also be a problem. The BBB can be disrupted by drugs, seizures, strokes, hypertension, head trauma, hyperthermia, extreme physical stress, brain infections, radiation, alkalosis and ischemia/hypoxia [26]. One can see that there may be disruption of the BBB in OSA as a result of hypertension and hypoxia, although this has not been directly tested. Lim et al. have written a recent review focusing on the multiple different possible pathways for how chronic intermittent hypoxia may damage the BBB. These include oxidative stress, angiogenesis, and molecular oxygen sensors [37]. Once the BBB is open, there is evidence that arterial hypertension may increase intracranial pressure; hypertension will increase hydrostatic capillary pressure. Any disruption of the BBB will by definition increase the risk of brain edema because of the changes in filtration volume and osmotic pressure [32]. Another mechanism for BBB disruption in OSA may be related to homocysteine levels. Homocysteine has been shown to be elevated in OSA patients [38] and may act as an excitatory neurotransmitter. It has been shown that homocysteine can disrupt the BBB by increasing oxidative stress and upregulating matrix metalloproteinases [22]. TNF-α (tumor necrosis factor alpha) is an inflammatory mediator which is increased in OSA. Surgical treatment of OSA has been shown to lower it [39] as has CPAP treatment [40]. There is a TNFα gene polymorphism which has been shown to be associated with higher TNFα levels and excessive daytime sleepiness in pediatric OSA [41]. TNFα has also been shown to be involved in opening the BBB and in contributing to brain edema [42]. This would be yet another mechanism for brain edema and BBB dysfunction in OSA that may contribute to higher ICPs. One must ask the question if the "excessive daytime sleepiness" seen in the TNFα polymorphism study might be a reflection of higher ICPs correlated with higher TNFα levels. Interestingly, Lim et al. point out research that indicates that obesity is a very strong stimulus for elevation of TNFα [37]; this could play a role in the link between obesity and IIH, if BBB permeability is indeed a significant factor in IIH, as is suggested here as a possibility. The fact that 77% of IIH patients have been found to have peripheral edema [8], may indicate that in IIH there is actually a systemic problem with the endothelial barrier. In conclusion, there are multiple biologically plausible mechanisms for how OSA may contribute to BBB dysfunction, and consequently brain edema and elevated ICP.

Hypercoagulation in IIH and OSA

In IIH there is a definite association with hypercoagulability, and there is a theory that IIH might be caused by micro-thrombus in the arachnoid granulations. Patients with IIH have been found to have a higher frequency of prolonged activated partial thromboplastin time, lupus anticoagulant, high plasminogen activator inhibitor activity as well as high lipoprotein A [43]. Anticardiolipin (ACL) antibody has been shown to be common in IIH [44]. OSA is known to lead to hypercoagulability in multiple ways, and is linked to venous thromboembolism as well as arterial thrombosis [45]. OSA is associated with increased blood viscosity, hematocrit, certain clotting factors, tissue factor, platelet activity and whole blood coagulability, as well as impaired fibrinolysis [46]. It has been shown that OSA is also associated with the presence of anticardiolipin (ACL) antibody, and that treatment of the OSA using CPAP or sleep surgery can lead to a decrease in the ACL antibody titer [47–48]. This leads to speculation regarding the etiology of hypercoagulability in IIH; could it be related to underlying OSA? Future studies using more accurate hypopnea criteria may help clarify the connection between these conditions.

A role for neural sensitization

Based on the above, it may be that OSA is instrumental in causing a hypercoagulable state which then leads to poor CSF drainage and a predisposition to increased ICP, adding to the brain edema, ventilatory and venous pressure factors. Glutamate may be playing a role here as well; it has been shown that injection of glutamate into the amygdala may induce hypercoagulation [49]. This is very interesting given what we know about the amygdala in learning and how this may affect the response to sleep disordered breathing. Long term potentiation (LTP) is the mechanism by which we learn, and how we develop a condition called neural sensitization [31]. Neural sensitization develops in response to a threat to the organism, in order to produce a more forceful response which will lead to protection from tissue damage [50]. LTP occurs by glutamate stimulation of the amygdala to produce these neurological changes [31]. Dr. Avram Gold has discussed a theory involving neural sensitization in sleep disordered breathing (SDB), suggesting that it occurs in SDB via a neurological response to pharyngeal collapse [51]. If this is true, then this is a mechanism via which the neurological stress response to apnea or impending pharyngeal collapse may generate glutamate in the amygdala in the attempt to arouse the individual so that they may protect their airway, while inadvertently also increasing their risk of thrombosis. This may also explain why Emin Akkoyunlu et al. found edema specifically in the amygdala in OSA [25], if this neural sensitization response is occurring in OSA and increasing glutamate in the

amygdala. This concept may also provide a link to the symptoms of multiple chemical sensitivity (MCS). Dr. Iris Bell has hypothesized that MCS may be a result of neural sensitization of the amygdala and limbic system to multiple chemicals, such that low levels of these chemicals may produce a response [52]. This is an accepted theory in environmental medicine. If chemical exposure leads to neural sensitization, then this would also be mediated via glutamate and therefore chemical exposure in MCS might cause both brain edema and hypercoagulation. In the setting of other risk factors previously discussed, chemical exposure could be a trigger for ICP elevation. Alternatively, one needs to consider the possibility, as recently proposed, that the neural sensitization present in MCS that contributes to its symptoms, may ultimately originate from underlying sleep disordered breathing [53].

Implications for treatment

The data on glutamate involvement in brain edema are compelling, and urge not only proper treatment of OSA but also avoidance of neuro-excitotoxin triggers including glutamate, aspartate and cysteine in the diet, as well as electromagnetic fields, especially for those with CSF drainage problems. Anti-depressants might attenuate glutamate release in response to triggers. Glutamate antagonism may be helpful. Definitive treatment of OSA may, in addition to resolving the ventilatory triggers for increased ICP, improve the hypercoagulability which might be playing a role in CSF drainage problems in IIH. Eradicating OSA might have a beneficial effect on neural sensitization, and might also reduce overall stress levels, as well as oxidative stress, homocysteine, and TNF-α. All of these factors might affect ICP, based on the data discussed here. Finally, there is evidence that CPAP may not be the best treatment for patients with OSA and IIH, due to its potential effects on ICP, such that Bi-level is a better option. When IIH is present, it may be that a definitive surgical solution for OSA, yielding an AHI of zero, would be the best option, and one which involves correcting the increased vertical development of the face might be ideal. Given the potentially significant contribution of OSA to intracranial pressure, it would be prudent to perform a thorough evaluation to rule out even mild OSA and treat this first prior to initiating invasive shunt procedures in IIH. (The exception would be if vision is imminently at risk.) Finally, if anatomical changes during early development may truly increase the risk of IIH in addition to that of OSA, then aggressive measures to reverse mouth breathing in childhood would be indicated.

Summary

This paper weaves together many facts into a complex paradigm for how obstructive sleep apnea may contribute to increased intracranial pressure and the condition of idiopathic intracranial hypertension. The relative importance of the many factors; hematological, anatomical, ventilatory, biochemical and neurological, may be difficult to determine. Future research will hopefully elucidate answers to some of the questions raised here, with the goal of improving the lives of those afflicted with idiopathic intracranial hypertension. Because this paper discusses a myriad of factors which may generate elevated intracranial pressure in obstructive sleep apnea, there are multiple hypotheses proposed, rather than one single hypothesis. These will be detailed below, with suggestions for further research.

Hypotheses proposed and how they might be tested

- Mouth breathing leading to increased vertical development raises the risk of IIH by narrowing the neck compartment to increase resistance in the internal jugular veins.

- Forward head posture may lead to compression of and increased resistance in the internal jugular veins, raising the risk of IIH.

Suggested experiment: perform a study examining facial structure, frequency of mouth breathing, and degree of forward head posture in IIH patients compared to controls. Correlate these factors with jugular venous resistance, as well as diameter of the jugular foramen as measured on CT. Comparing airway diameter as seen on MRI to jugular venous flow may also show a correlation between neck compartment space, OSA risk and IIH.

- Obesity contributes to IIH by narrowing the space in the neck compartment needed for the jugular veins.

Suggested experiment: measure jugular venous resistance before and after weight loss. Compare this to central venous pressure before and after weight loss, to assess the confounding effect of abdominal obesity transmitted to jugular venous pressure. Compare to a control group, which should show fewer changes in the jugular veins with weight loss.

- Glutamate neuro-excitotoxicity mediates the brain edema seen in IIH and OSA.

Suggested experiment: perform studies looking at brain glutamate activity using proton magnetic resonance spectroscopy on patients with IIH and OSA, comparing to normal controls. This will show that glutamate over-activity is present in patients with IIH and OSA. To demonstrate that there is a direct relationship to brain edema may be more difficult, but one could attempt to show a quantifiable difference correlating the degree of edema to the amount of glutamate over-activity. If there are multiple factors contributing to the brain edema in IIH, then this study may not yield positive results even if there is a relationship between glutamate over-activity and brain edema in these patients. Choosing thin patients with IIH might remove a possible confounder if obesity contributes to brain edema via TNFα levels and BBB dysfunction.

- CPAP and possibly Bi-level may increase ICP more so in those with IIH than in normals.
- A PAP machine can increase ICP in IIH patients due to its EMF.

Suggested experiment: this will be a very difficult hypothesis to prove. Treating OSA should lower ICP, therefore using CPAP may not show an increase from baseline. It would have to be compared in each individual to a different method of OSA treatment that would not be expected to increase ICP, but be comparable to CPAP in its ability to treat OSA. If a patient population with IIH and no OSA could be trialed on CPAP, then this might work. This would then need to be compared to a control group without IIH. For the EMF part of this experiment, patients with IIH can go one night with Bi-level with the machine next to the head, within a measureable EMF, and another night with the machine far from the head outside of a measurable EMF, with ICPs measured in the morning after each night. If positive results are obtained, this will have greater implications for the effect of any EMF on an IIH patient, and may suggest an etiologic diagnosis for those patients claiming to have EMF sensitivity.

- OSA disrupts the blood–brain barrier via multiple mechanisms and contributes to brain edema in this manner.

Suggested experiment: animal models could be developed to test this hypothesis.

- BBB dysfunction is prominent in IIH

Suggested experiment: measure BBB function in IIH patients vs. controls.

- The hypercoagulability seen in IIH may be secondary to underlying OSA.

Suggested experiment: test a group of IIH patients with hypercoagulability using the most sensitive hypopnea criteria and instruments, to confirm that all of these patients will have underlying OSA. Compare this to the prevalence of hypercoagulability in a group of IIH patients without OSA. This still will not prove causation, which may be difficult to show.

Conflict of interest statement

The author claims no conflict of interest in the writing of this paper.

Table of abbreviations

ACL	anticardiolipin
AHI	apnea-hypopnea index
BBB	blood–brain barrier
CPAP	continuous positive airway pressure
CSF	cerebrospinal fluid
EMF	electromagnetic field
ICP	intracranial pressure
IIH	idiopathic intracranial hypertension
LTP	long term potentiation
MCS	multiple chemical sensitivity
OSA	obstructive sleep apnea
NMDA	N-methyl-D-aspartate
REM	rapid eye movement
SDB	sleep disordered breathing
TNFα	tumor necrosis factor alpha

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