Medical Hypotheses 83 (2014) 792–797

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

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

D.E. Wardly *

7901 Autumn Gate Ave., Las Vegas, NV 89131, United States

ARTICLE INFO

Article history:
Received 16 February 2014
Accepted 14 October 2014

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 neuroexcitotoxicity, 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.

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-

☆ *Sources of funding:* This project was completely self-funded by the author.
* Fax: +1 505 212 1712.
E-mail address: deborahwardly@yahoo.com

http://dx.doi.org/10.1016/j.mehy.2014.10.011
0306-9877/

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