Prevalence of elevated intracranial pressure in patients with classical trigeminal neuralgia with overweight and obesity

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Abstract

Background: There is a clear association between obesity and Idiopathic Intracranial Hypertension (IIH), a syndrome characterized by increased Intracranial Pressure (ICP). The clinical manifestations of IIH include headache and visual/oculomotor disorders due to the involvement of abducens nerve. Thus far, it has not been widely studied whether affections by ICP elevation could involve other cranial nerves such as the trigeminal nerve.

Objective: The aim of this study is to analyze the prevalence of elevated ICP in patients with BMI ≥ 25 that suffer vascular compression of the trigeminal nerve.

Methods: A case series including 19 patients evaluated during a period of 8 months with BMI ≥ 25 and a clinical diagnosis of classic trigeminal neuralgia (TN) who underwent Microvascular Decompression (MVD) surgery is reported. Patients with TN presenting another cause of intracranial hypertension were excluded. The ICP was determined just before MVD surgery by introducing an enteral tube through a 2 mm incision in the dura and measuring the level reached by the CSF.

Results: In our series, 42.1% of patients suffered overweight (n = 8), 47.3% grade I obesity (n = 9) and 10.5% grade II obesity (n = 2). The ICP was elevated in 47.4% of patients.

Conclusion: IIH is an obesity-related disorder. Patients with BMI ≥ 25 and TN show a high prevalence of ICP. It is important to consider that an obese patient may present high ICP during and after MVD surgery.

Keywords: body mass index, idiopathic intracranial hypertension, trigeminal neuralgia, pseudotumor cerebri, obesity.
Introduction

The global prevalence of overweight and obesity has increased dramatically in recent decades. The current obesity and overweight epidemic is associated with lifestyle, as well as genetic and environmental aspects \(^{(1)}\). Obesity rates increase regardless of age, sex, geographical locality, ethnicity or socioeconomic status. Nearly a third of the world's population is now classified as overweight or obese \(^{(2)}\). As a complex multifactorial disease, obesity is directly related to the development and evolution of a wide spectrum of co-morbidities, including type 2 diabetes mellitus, dyslipidemias, non-alcoholic fatty liver disease, respiratory abnormalities, osteoarticular diseases, psychiatric conditions, reproductive dysfunction, certain types of cancer, cardiovascular disease and hypertension \(^{(3,4)}\).

Idiopathic Intracranial Hypertension (IIH) also known as Pseudotumor cerebri, is a disorder characterized by increased Intracranial Pressure (ICP) with no apparent cause. It was first described by Quincke at the end of the 19th century naming it "Serous Meningitis", referring to the presence of Intracranial Hypertension (ICH) without hydrocephalus or space occupying lesion \(^{(5)}\). The symptoms of IIH include: headaches, transient or persistent vision loss, papillae edema. Idiopathic Intracranial Hypertension (ICH) without hydrocephalus or space occupying lesion \(^{(5)}\). The symptoms of IIH include: headaches, transient or persistent vision loss, papillae edema. Idiopathic Intracranial Hypertension (ICH) without hydrocephalus or space occupying lesion \(^{(5)}\). The symptoms of IIH include: headaches, transient or persistent vision loss, papillae edema. Idiopathic Intracranial Hypertension (ICH) without hydrocephalus or space occupying lesion \(^{(5)}\). The symptoms of IIH include: headaches, transient or persistent vision loss, papillae edema. Idiopathic Intracranial Hypertension (ICH) without hydrocephalus or space occupying lesion \(^{(5)}\). The symptoms of IIH include: headaches, transient or persistent vision loss, papillae edema. Idiopathic Intracranial Hypertension (ICH) without hydrocephalus or space occupying lesion \(^{(5)}\). The symptoms of IIH include: headaches, transient or persistent vision loss, papillae edema.

Table 1. Modified Dandy Diagnostic Criteria for Idiopathic Intracranial Hypertension

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<th>Modified Dandy Criteria</th>
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<td>1.- Signs and symptoms of intracranial hypertension (headache, nausea, vomiting, transient vision loss, papillae edema).</td>
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<td>2.- Absence of signs of neurological focality, except for unilateral or bilateral paralysis of VIth cranial nerve.</td>
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<td>3.- Increased CSF pressure without chemical or cytological abnormalities.</td>
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<td>4.- Neuroimaging studies do not reveal alternative causes or intracranial hypertension.</td>
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<td>5.- Conscious and alert patient.</td>
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An oculomotor affection of the abducens nerve is a common finding during IIH classically causing binocular horizontal diplopia that worsens with long-distance viewing. The gold standard for diagnosing elevated ICP is either a lumbar puncture or a direct intracranial measurement through a craniotomy. A normal ICP is considered between 7 - 15 mmHg, while 20 - 25 mmHg is postulated as the upper limit of normal and sometimes may require therapeutic intervention \(^{(11,12)}\). The causes of IIH are still debated although obesity and weight gain are clearly established as risk factors. Initially, the most accepted hypothesis proposed that the central fat increased intra-abdominal pressure, generating an elevation in the central venous pressure and subsequently intracranial venous pressure. This hypothesis was refuted by Kesler, since most of the patients with IIH had a higher proportion of fat in the lower body than central obesity \(^{(13)}\). Another theory unifies various effects on the mineralocorticoid receptor (MR) to explain a possible mechanism that triggers an increased production of CSF and consequently the ICP during IIH \(^{(14)}\). The MR is abundantly found in the choroid plexus epithelium, regulating the
production of CSF. Activation of MRs or their downstream pathways can stimulate the Na+/K+-ATPase to transport sodium ions in the apical membrane of the choroid plexus towards cerebral ventricle creating an osmotic gradient to enhance CSF secretion and therefore increasing ICP\(^{15}\). Cortisol levels in CSF are regulated by the 11-ß-hydroxysteroid dehydrogenase, abundant in the choroid plexus that converts inactive cortisone into cortisol, which shows great affinity to MR\(^{16}\). The corticosteroid axis disorders, through exogenous or endogenous stimuli, can lead to development of IIH through this mechanism.

Human fat, an active endocrine tissue, secretes mineralocorticoid releasing factors, providing another possible link for ICP elevation in obese patients with IIH\(^{16,17,18}\). Another hypothesis about IIH pathophysiology focuses on the insufficiency of jugular vein valves and its potential to facilitate the pressure transmission contributing to intracranial hypertension\(^{19}\). Moreover, during obstructive sleep apnea that is often associated with obesity, it has been described that hypoxia and hypercapnia result in cerebral vasodilation that causes an increase in ICP that can be maintained if there is sufficient compression of the venous sinus\(^{20,21}\). In summary, conditions associated with obesity can be factors to consider for the development of IIH. Nevertheless, the precise pathogenesis of IIH is not known exactly, multiple coexisting mechanisms are needed to consider the presence of this syndrome (Table 2).

The association between IIH and Trigeminal Neuralgia (TN) has been slightly reported. Some cases where IIH was accompanied by a clinical presentation of TN and were solved by lumbar puncture and pharmacological treatment with acetazolamide and/or gabapentin. The relation between the reduction of CSF pressure and the improvement of TN symptoms and signs, suggests the possibly of a pressure-related phenomenon that induces neurovascular conflict\(^{22,23,24}\).

### Table 2. Main mechanisms involved in IIH pathogenesis.

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<th>IIH Pathogenesis</th>
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<td>1. Elevation of intracranial venous pressure due to stenosis of the venous sinuses.</td>
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<td>2. Increase in CSF production and increased resistance in its absorption.</td>
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<tr>
<td>3. Increased venous pressure abdominal and intracranial in obesity.</td>
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<td>4. Alternation in the mechanisms of water and sodium retention.</td>
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<td>5. Conscious and alert patient.</td>
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TN is a disease characterized by sudden, severe, periodic, stabbing, lancinating and electric shock-like pain attacks that are usually one-sided and occurs specifically on the trigeminal nerve distribution of the face. The paroxysms of severe pain can be associated to one or more branches of the nerve with periods of remission and exacerbation of pain\(^{25}\). TN has a prevalence of 1-2 per 10,000 habitants and an incidence that varies from 4-5 cases per 100,000/year reaching 20 per 100,000/year after the age of 60. It can be developed at any age and occurs more frequently in women than in men with a ratio of 3:2\(^{26}\). According to a recent classification, TN is divided into classical, secondary and idiopathic\(^{27}\). For the purposes of this research, we focused on studying only the classical form. Classical TN occurs in multiple episodes throughout the day of short duration. However, attacks may occur more frequently, becoming more intense and the characteristics of the pain change, indicating a progressive nature of the disease. The etiologic of classical TN is due to chronic compression of the trigeminal nerve at the root entry zone; this compression may be caused by tumors or more frequently by blood vessels.
The most often implicated vessels include: superior cerebellar artery, anterior inferior cerebellar artery and superior petrosal vein complex with multiple tributaries. The diagnosis of the disease can be supported with a MRI. However, certain studies have shown that the MRI has a sensitivity of 52% for diagnosing neurovascular contact of the trigeminal nerve. The initial treatment of TN is pharmacological, carbamazepine or oxcarbazepine are first line therapy. Other drugs such as gabapentin, phenytoin, pregabalin, lamotrigine, baclofen and botulinum toxin-A are alternative treatments. Surgical options are available if medications are no longer effective or tolerated. Percutaneous Rhizotomies (PR), Stereotactic Radiosurgery (SRS) and Microvascular Decompression (MVD) are the most promising surgical alternatives. The MVD surgery procedure requires the establishment of a microsurgical site that involves a craniotomy and the opening of the dura; procedure that allows the CSF to be obtained or manipulated to determine some of its parameters. The aim of this study is to analyze the prevalence of high ICP in patients with BMI ≥ 25 that suffer vascular compression of the trigeminal nerve.

Methods
We selected 97 patients with diagnosis of TN treated at our medical center between December 2017 and August 2018 who underwent MVD surgery. All of them were diagnosed with TN based on clinical criteria and vascular compression of the trigeminal nerve was confirmed by MRI 3D-FIESTA sequence (Signa; GE Medical Systems, Milwaukee, WI, USA). We excluded patients with BMI < 25; with idiopathic and secondary TN (epidermoid cyst, post-herpetic, meningioma, multiple sclerosis), patients under medication that could condition IIH (hypervitaminosis, tetracyclines, nalidixic acid, nitrofurantoin, sulfonamides, retinoids, cinetidine, cyclosporine, diphenylhydantoin, lithium carbonate, danazol, tamoxifen, corticosteroids, anabolics and growth hormone); those which had some disease related to secondary IIH (hypothyroidism, hypoparathryidism, Cushing’s syndrome, deficiency anemias, chronic renal failure, Addison’s disease); patients with any disease that could manifest CSF abnormalities or with CSF leakage prior to sampling or during sample collection due to technical incidents. We also excluded patients with abnormal imaging studies (ventriculomegaly or intracranial tumors) and patients older than 65 years as they could have cerebral atrophy which favors an increase in ICP. After considering our inclusion and exclusion criteria, our series comprised 19 cases. ICP was determined for all patients under general anesthesia before MVD surgery. For the measurement, the patient was placed in a lateral decubitus position, trichotomy and antisepsis were performed at the retroauricular region followed by a minimally invasive retrosigmoid craniectomy. A 3 mm incision in the dura was then performed where approximately 5 mm of a 5 Fr enteral feeding tube was gently inserted at an angle of 45º to position it between the dorsal surface of the cerebellum and the internal face of the adjacent dura and directed towards the cistern of the bulbopontine sulcus. The CSF flows up through the probe placed in a totally vertical position and when the CSF movement stabilized, the level reached was determined using a sterilized measuring tape. Subsequently, a CSF sample was collected for biochemical and cytological analyses. The following values for ICP were used as reference: < 7 - 15 cmH₂O = Normal; 20-25 cmH₂O = Inconclusive; and ≥ 25 cmH₂O = High.
The weight and height of each patient were measured with a mechanical scale and a RGZ-160 stadiometer. The patients were followed up in the immediate postoperative period and with consultations at one month, three months and one year after surgery. Statistical analyses were performed with SPSS 22.0 software (IBM Corporation, Armonk, New York, USA). Central tendency measures were established and a Pearson correlation coefficient between BMI and ICP was obtained.

Figure 1. (A) Patient preparation for MVD surgery. (B) Minimally invasive retrosigmoid craniectomy before incision in the dura. (C) Enteral feeding tube colocation for ICP determination. Red arrow indicates de level reached by the CSF.

Results
Of the 19 patients, 89.5% were women and 10.5% men, with an age range between 26-59 years (M = 47). It was determined that 42.1% of these patients were overweight (n = 8), 47.4% grade I obesity (n = 9) and 10.5% with grade II obesity (n = 2). After ICP analysis, 37.8% of our patients had a normal ICP (n = 7), 15.8% were inconclusive ICP (n = 3) and 47.4% showed high ICP (n = 9). The mean ICP was 14.4 cmH2O for normal value, 20.0 cmH2O for inconclusive and 27.7 cmH2O in the case of high ICP. Graph 1 demonstrates a certain tendency of the ICP to rise according to the increase in BMI; Pearson’s correlation coefficient was +0.122 (p = 0.618). On the other hand, the analysis of CSF samples showed positive for the presence of countless erythrocytes in all the samples, probably secondary to a traumatic puncture and the implicit surgical procedure. Furthermore, all the samples showed elevated proteins, glucose and DHL. VDRL and Gram staining in CSF were negative in all cases.

Graph 1. Correlation between intracranial pressure and body max index

During MVD surgery, we found that the neurovascular contact was arterial in 4 cases, venous in 8 and mixed in 7. The most commonly involved artery was the superior cerebellar artery (n = 7), followed by the vertebrobasilar artery (n = 4) and the anterior inferior cerebellar artery (n = 2), while the most commonly involved veins were the pontine vein (n = 6), an innominate vein (n = 5), ponto-trigeminal (n = 3), superior petrosal venous complex (n = 2) and bridging vein (n = 1).

After the follow-up period, 78.9% of patients (n = 15) had a complete remission of pain and 21.1%...
(n = 4) presented recurrence of pain during the first post-surgical year, however all the recurrences were treatable with a pharmacological approach.

**Conclusion**

Our study suggests that a high percentage of patients with BMI ≥ 25 and TN suffer of elevated ICP without apparent cause. Although the ICP raised according to the increase in BMI and a positive Pearson's coefficient, the correlation was non-statistically significant (p = 0.618). Some of the limitations of the study include the relatively low number of patients and the absence of patients without overweight/obesity as control.

A positive feedback loop is often proposed for ICP where constriction in transverse sinuses raises venous pressure, decreasing CSF resorption and subsequently elevating the ICP. We observed that some patients with IIH showed a reduction in the volume of the cerebellopontine angle cistern where the trigeminal nerve and adjacent vascular structures are located, this reduction could be favoring the neurovascular contact, being the superior cerebellar artery and pontine vein the vessels more frequently involved. Therefore, we think that cistern volume reduction could be a consequence of an increase of global retrograde venous pressure in brain tissues in a phenomenon analogous to venous stasis of the lower limbs in obese patients. Another important point to mention is that none of the patients with IIH presented its characteristic signs or symptoms, however, it is possible that these were masked by the trigeminal pain syndrome. Moreover, it is necessary to demonstrate the absence of CSF alterations for IIH diagnosis. All patients in our series showed an increase in CSF cell count although we assume that this anomaly may be secondary to the technique required to obtain the sample. CSF analysis should be an important point to consider for following studies in our group.

As mentioned, due to the limitations of the observational nature of our study, we believe that cohort or control-cases studies are needed to clearly determine the association between IIH and TN. If this association could be proven, the prevention and management of obesity may be considered in the treatment of patients with TN and could support the hypothesis that IIH could be a factor involved in the pathophysiology of TN.

**Founding**

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**Conflict of interest**

The authors declare having no conflicts of interest.

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