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REVIEW ARTICLE

# Dural sinus collapsibility, idiopathic intracranial hypertension, and the pathogenesis of chronic migraine

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## Abstract

Available evidences suggest that a number of known assumption on idiopathic intracranial hypertension (IIH) with or without papilledema might be discussed. These include (1) the primary pathogenetic role of an excessive dural sinus collapsibility in IIH, allowing a new relatively stable intracranial fluids pressure balance at higher values; (2) the non-mandatory role of papilledema for a definite diagnosis; (3) the possibly much higher prevalence of IIH without papilledema than currently considered; (4) the crucial role of the cerebral compliance exhaustion that precede the raise in intracranial pressure and that may already be pathologic in cases showing a moderately elevated opening pressure; (5) the role as "intracranial pressure sensor" played by the trigeminovascular innervation of dural sinuses and cortical bridge veins, which could represent a major source of CGRP and may explain the high comorbidity and the emerging causative link between IIHWOP and chronic migraine (CM). Accordingly, the control of intracranial pressure is to be considered a promising new therapeutic target in CM.

**Keywords** Sinus stenosis · Idiopathic intracranial hypertension · Bridge vein · Self-limiting venous collapse · Chronic migraine · Starling resistor

## Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (IIH) is a disorder characterized by a raised intracranial pressure without a detectable cause [1]. Its typical clinic profile includes headache, usually on daily basis, transient visual obscuration, diplopia, papilledema, vertigo, tinnitus, back pain [2], and allodynia [3]. This condition, even if considered "benign", may lead to permanent visual loss in up to 25% of cases [4] if left untreated. Current incidence of IIH is about 2.4 per 100,000 in the general population. Female sex, obesity, and sleep disturbances represent the major risk factors for IIH development [5]. In obese 15–44-year-old women, IIH incidence rises up to 22/100,000 [6]. However, the condition is not infrequent in children [7] and men with IIH present a doubled risk to develop severe visual loss [8]. IIH may present with a chronic unremitting pattern, but a periodic recurrent course is common, as well [9]. Recurrences may follow weight gain and have been observed during pregnancy [10]. The most specific neuroradiological markers of IIH are dural sinus stenosis, empty sella, increased cerebrospinal fluid (CSF) in the subarachnoid space of optic nerves, and ocular globe flattening. These have been included into the last revision of IIH diagnostic criteria [11]. Secondary forms of raised intracranial pressure (ICP) may be attributed to cerebral venous thrombosis [12] and to some medical treatments (minocycline and tetracycline, growth hormone, steroids, and vitamin A, among others) or have been documented in the course of systemic diseases [1].

Despite the advancement of research in recent years [1, 13, 14], IIH pathogenesis remains poorly understood. A plausible pathogenetic theory should explain the high prevalence in female sex and in obese people, the presence in almost all the cases of dural sinus stenosis [15,

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16] that may reopen after CSF subtraction [17, 18], the remission of the symptoms with ICP normalization that follows endovascular stenting of dural sinus [19], and the extraordinary identity in clinical presentation with chronic migraine (CM), with which it is very frequently misdiagnosed [20–22] and in particular with refractory forms with which it shares the high prevalence of venous stenosis [23–25] and some phenotypic characteristics of pain such as nocturnal attacks and the worsening of pain in the recumbent position [26]. Finally, since CSF production rate (about 0.2–0.4 ml/min) [27] is faster enough to allow its turnover up to 4 or 5 times a day, a valuable pathogenetic theory of IIH should also clarify the symptomatic remission that commonly follows a single lumbar puncture (LP) with CSF subtraction, lasting up to many months [17, 23, 25, 28] and therefore not easily attributable to a late closure of the dura mater puncture.

## Idiopathic intracranial hypertension without papilledema

IIH may present without papilledema (IIHWOP) in a part of the patients. IIHWOP has been so far considered an infrequent variant of IIH [29, 30] with an unknown population prevalence. Actually, a raised ICP is not the only variable influencing the onset of papilledema. According to Pascal's law, a fluid pressure in a closed space should be the same in every point. However, papilledema and visual defects may be unilateral [31] or markedly asymmetric in up to 10% of the patients [32, 33] and this finding is related to the caliber of the optic canals but not with the disease duration [33]. A recent ICP monitoring study confirmed that the mean ICP threshold for the development of papilledema is very variable among different individuals [34]. These findings suggest that a narrow optic canal may prevent the development of papilledema in some patients.

The opening pressure (OP) in IIHWOP is lower than in IIH [34, 35] albeit monitoring studies have demonstrated that ICP is unstable in these patients, due to large intraday fluctuations, mainly nocturnal, encompassing the upper limit of the normality [26, 31, 36]. However, current diagnostic criteria for IIHWOP [11] do not take into account the typical mild elevation and the fluctuations of CSF pressure showed by this condition [23, 25, 34, 35] and still require the demonstration of an OP > 250 $mmH_2O$ for IIHWOP diagnosis.

Taken together, the above considerations raise concerns about a possible exceedingly low sensitivity of IIHWOP current diagnostic criteria [37–39]. Accordingly, if the presence of papilledema remains a highly specific sign of IIH, its absence does not exclude the diagnosis, instead it may reflect a milder (or intermittent) intracranial hypertension and/or the coexistence of protective factors.

## Which is the true prevalence of IIHWOP?

IIH may occur without headache in non-migrainous individuals or in the course of a strong migraine protective factor like pregnancy [40]. Therefore, in subjects lacking both, papilledema and continuous headache, the condition may run almost asymptomatically or can be misdiagnosed because of atypical clinical presentations such as fibromyalgia [41], stabbing headache [42, 43], headache associated with cough, physical efforts or sexual activity [44], or with recurrent epistaxis [45] and chronic fatigue syndrome [46]. Recently, we have found that signs and symptoms of endolymphatic hydrops are included in IIH/IIHWOP clinical presentation and remit after CSF withdrawal by LP [47], a finding that might represent the link between migraine and vestibular symptoms. Taken together, all the above considerations highlight that IIHWOP diagnosis is easily overlooked and that its true population prevalence may be significantly underestimated [48]. Actually, a well-conducted study has demonstrated that an OP > 200 $mmH_2O$ may be found in at least 11% of individuals with bilateral sinus stenosis without other signs or symptoms of intracranial hypertension [49]. This means that the prevalence of an asymptomatic sinus stenosis–associated raised ICP is about one thousand times higher than that of IIH (2.4–22/100,000) [6]. Clinical presentation of IIHWOP may be indistinguishable from CM [20]. Actually, an IIHWOP has been diagnosed in 10–14% of unselected series of CM [21, 22] and in 22.5–86.4% [23, 26, 40] of refractory CM series, confirming that IIHWOP prevalence in CM patients is extraordinarily higher than expected. Based on the above considerations, we have recently proposed [50] that a clinical and epidemiological "continuum" might exist between (a) IIH with papilledema, an infrequent condition probably representing only the visible part of a disorder with a much higher prevalence [51]; (b) IIHWOP, presumably largely misdiagnosed and/or underdiagnosed at the present; and (c) asymptomatic sinus stenosis–associated intracranial hypertension, a silent condition highly prevalent among "healthy" individuals.

## Routes of CSF reabsorption

Increased dural sinuses pressure (DSp) is an "universal mechanism in pseudotumor cerebri of varying etiologies" [52] and represents the common final pathway of different mechanisms that, by reducing the pressure gradient between CSF pressure (CSFp) and DSp, leads to the reduction of CSF absorption through arachnoid villi and granulations (AGs). However, in recent years, the role of AGs as the prevalent CSF drainage pathway has been questioned and alternative ways of CSF discharge have been described [53–56]. A pathway of CSF circulation through the cerebral parenchyma called "glymphatic system" [57] has recently been documented.

The glymphatic system contributes to exchange the brain interstitial fluid and to remove metabolic products, accounting for a relevant CSF outflow through lymphatics and perinervous spaces, mainly at the olfactory level. This CSF drainage route may account for up to 48% of the total amount in the sheep [58].

The spinal compartment is another accessory site of CSF discharge. Periradicular lymphatic collectors and typical AGs have been described in almost all the thoracic and lumbar root nerve exits [59]. According to recent studies [53], the CSF outflow at the mentioned sites of the spinal compartment is about 0.11 ml/min at rest but may increase up to 0.22 ml/min with physical activity, i.e., almost up to one half of the CSF production rate.

### The physiologic significance of arachnoid villi and granulations

Based on animal studies, under conditions of normal or low ICP, the CSF can be reabsorbed almost entirely by the alternative discharge routes previously described, with minimal involvement of the AGs [60]. However, the amount of CSF leaving the craniospinal space through the AGs grows parallel to the ICP [60]. The AGs are more represented in the dural venous system of the subjects with IIH as a sort of a compensatory mechanism [61]. This suggests that the alternative CSF discharge pathways, as a whole, might have an easily saturable flow rate and could not adapt to the ICP increments without showing a symptomatic overflow [62]. On the contrary, the flow through the AGs is linearly related to the sinus transmural pressure, up to high ICP values [63]. Thus, AGs cannot be considered the main CSF outflow route but remain crucially important in CSF volume and pressure control.

## Dural sinus stenosis

Dural sinus stenosis is strictly associated with IIH and represents a reliable diagnostic marker with 93% specificity and sensitivity [15]. Morphology of sinus stenosis may be divided into intrinsic (hyperplastic AGs, segmental hypo/aplasia, venous septa, or mural thrombosis) or extrinsic (smooth tapered appearance resulting from external compression by hypertensive CSF). Many patients carry multiple stenoses of both kinds. Regardless of their conformation, there is evidence of a venous pressure gradient across the stenosis responsible for a reduction of CSF reabsorption that leads to ICP increase [64]. Extrinsic stenosis may improve or resolve after CSF diversion or subtraction by LP [17, 65–67], with immediate resolution of symptoms and pressure gradient normalization [64, 68]. Stenosis may persist despite treatment of raised ICP, suggesting their "fixed" nature [69]. However, according to a recent study, the entire sinus venous tree is compressed in the course of IIH and enlarges after LP, even in subjects not showing a stenosis reopening [70]. Also, sinus venous stenting is considered an innovative therapeutic option with a high rate of immediate remission in IIH [71, 72], suggesting that sinus narrowing is involved in IIH mechanisms.

## Cortical bridge veins as Starling resistors in cerebral perfusion control

To understand the role of venous stenosis in the IIH mechanisms, it is necessary to place them in the broader context of the brain perfusion. We have extensively reviewed the main available evidences supporting the pivotal role of the venous side of brain circulation in the cerebral perfusion autoregulation mechanisms [73]. These are briefly summarized below.

### The CSF pressure must be lower than cortical veins pressure

A critical role in the cerebral perfusion control is carried by the cortical bridge veins (BV). Besides the known ICP changes related to the body position, in subjects showing normal ICP at rest, the Valsalva maneuver induces the raise of ICP well beyond the normal limits, up to a mean of 323 $mmH_2O$ (range 260–470) [74]. In the absence of a compensatory mechanisms, these abrupt pressure changes in CSF pressure would compress the cortical veins whose internal pressure is only a few millimeters of mercury higher than CSF pressure [75]. This should never occur, as it would compromise the cerebral perfusion.

The BV represent the terminal of the cortical vein before joining the dural sinus. It has thin and non-muscular walls and is fully immersed in the CSF. Therefore, its caliber is functionally modulated by the transmural pressure, i.e., the difference between the internal venous pressure and the CSF pressure. Available evidences [73, 75–79] indicate that BV are not a passive blood collector but behave like a regulator of the venous discharge into the dural sinuses. Bridge vein behavior is perfectly described in terms of Starling resistors (SR), a fluid dynamic construct that governs the flow in flexible tubes immersed in a fluid with variable pressure. Accordingly with SR properties [73], when the CSF pressure equalizes that of cortical vein, i.e., when the transmural pressure approximates to zero, the distal extremity of the SR (i.e., the BV) starts to collapse reducing its caliber (Fig. 1). This leads to the immediate and parallel increase of pressure of the cortical vein upstream the stenosis and guarantees that the cortical vein pressure is always maintained a few millimeters of mercury above the CSF pressure, preventing its collapse. At the same time, the velocity of blood increases in the semi-collapsed BV, maintaining the flow rate unchanged. In an animal study, the experimental raising of ICP up to non-

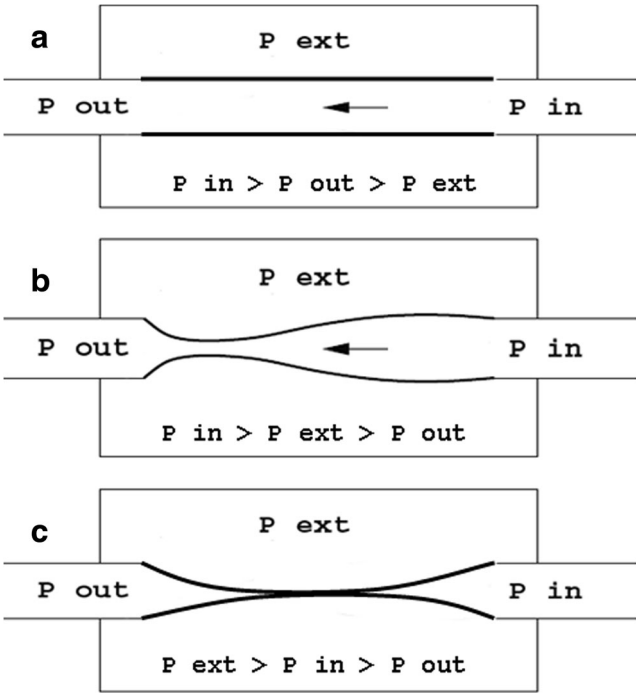


**Fig. 1** The shape of a collapsible tube exposed to an external pressure (extP). **a** If extP is lower of both, the input (inP) and the output pressures (outP), the tube is fully open. **b** If extP is lower than inP but higher than outP, the tube is partially collapsed at the distal end. **c** If extP is greater than inP, the tube is fully collapsed and the flow is arrested

physiologic values was followed by the synchronous and parallel rise in the CVp with a correlation coefficient of 0.98 [76] which is an uncommon value in biology. This finding, confirmed by many experimental observations [75–79], indicates that in healthy subjects a venous collapse does not occur even under non-physiological ICP increments, close to systemic arterial pressure. The SR properties of BV has been very recently replicated in a working physical model of brain perfusion and CSF circulation [80].

## Arteriolar pressure compensation

The CVp raise induced by the BV collapse requires a correspondent increase of the arteriolar pressure (Ap), in order to keep the perfusional pressure (Ap-CVp) unchanged. There is evidence that the experimental raise of ICP is promptly followed by a significant dilation of arteriolar caliber [81, 82]. Also, the arteriolar tone is dependent by the transmural pressure and is mediated by the direct myocytes activation by mechanoreceptors of the arteriolar wall (the myogenic response) [83]. When the Ap raises, the arteriolar transmural pressure increases triggering the myogenic response that reduces the arteriolar caliber. Conversely, the ascent of ICP will reduce the arteriolar transmural pressure. This will reduce the myocytes tone and will lead to the dilation of the arteriolar caliber. Thus, an ICP raise induces a dimensionally correspondent increase of both the CVp (mediated by the increase of BV collapse) and of Ap (mediated by a reduction of arteriolar transmural pressure) [73]. This is probably a key mechanism in cerebral perfusion autoregulation, aimed to keep unchanged the difference between the inlet and the outlet pressure of the perfusional bed, ensuring a constant cerebral blood flow in spite of the large daily physiological ICP fluctuations [73].

## The CSF pressure must be higher than dural sinus pressure

A second fundamental effect of the partial BV collapse, deeply involved in the homeostasis of the CSF volume and pressure, is termed "waterfall effect" [84]. The partial collapse of the BV also induces a sharp fall of the venous pressure immediately downstream the confluence with the dural sinus [76, 85, 86]. The finalistic purpose of the waterfall effect is to keep the dural sinus pressure (DSp) lower and "dissociated" from that of the cortical veins, despite the physical continuity of the two venous segments, so allowing the maintenance of the appropriate pressure gradient between ICP and DSp necessary to keep the CSF discharge rate perfectly balanced with its production rate. Due to the constancy of CSF production rate [87], even transient reductions in the waterfall effect would reduce the CSF outflow through the AGs, leading to the increase of CSF volume and pressure. In other words, once beyond the partially collapsed BV, the DSp is no more affected by the vis a tergo, from which it appears dissociated, and reflects, instead, only the right atrial pressure, i.e., the central venous pressure. In this way, the DSp is maintained always significantly lower than the cortical vein pressure (CVp) while the CSF pressure can always remain between the two. As the CSF outflow rate linearly correlates with the DSp/CSFp gradient [63], a DSp close to the central venous pressure guarantees that the CSF can leave the craniospinal space at the speed requested to balance its production rate without having to reach a too high pressure, such as to compress the cortical veins. Intriguingly, this balance is rigorously maintained without the need of any biochemical or neural control, similarly to a full tank that overflows exactly the same quantity of water coming from the tap.

## Hierarchies of intracranial fluids pressures

Based on the above considerations, the pressures of intracranial fluids, while constantly fluctuating, maintain a rigid hierarchical relationship in which arteriolar pressure > cortical vein pressure > CSF pressure > dural sinus pressure [88]. Only if these conditions are met the venous circuit remains patent, the correct balance between the production and excretion rates of CSF is maintained, and the system is stable.

### Necessity of dural sinuses rigidity

It should be emphasized that the maintenance of the waterfall effect implies two additional conditions. One is that the dural sinuses are dimensionally redundant, so that transient cerebral blood flow increases (such those occurring in migraine [89]) can be tolerated without resulting in an "insufficiency" of the dural venous system, which would entail a rapid impairment of the waterfall effect. The other, even more relevant, is that the dural sinuses are rigid enough to not collapse under CSF pressure increases. In the presence of an excessive distensibility of the dural sinuses walls the DSp would increase parallel to ICP [73] reducing the waterfall effect up to its suppression. In subjects with normal OP, the Valsalva effect is associated to large ICP waves, up to 470 $mmH_2O$ [74]. Therefore, the dural sinus wall is physiologically exposed to ICP values well beyond the upper limit of the normal range, fixed at 250 $mmH_2O$ [11]. The limited collapsibility of normal dural sinus, confirmed by direct pressure measurements [75, 76, 86], largely depends on its anatomical prismatic shape, with a side attached to the bone and the two others made of inextensible dura mater (DM) (Fig. 2). Interestingly, a very recent study on the mechanical properties of the porcine dura mater has demonstrated a significantly increased collagen content and a much higher mechanical stiffness of DM at the sagittal superior sinus level than in any other site of the skull [90]. Actually, study findings indicate that the dural sinus is rigid enough not to be affected by the experimental raise of CSF up to the fully non-physiologic value of 1000 $mmH_2O$ [76].

### Finalistic meaning of the dural sinus rigidity

A low collapsibility degree of the dural sinus ensures that its internal pressure, which is already dissociated from that of the cortical veins due to the bridge vein–dependent waterfall effect, also remains independent from the fluctuations of external CSF pressure, therefore reflecting only the right atrial pressure. This maintains an optimal pressure gradient for the CSF outflow through the AGs. Ultimately, the rigidity of the dural sinuses has the crucial finalistic significance of preserving the correct hierarchies of intracranial fluids pressures, a condition required to keep the correct brain perfusion balance, controlling and stabilizing at the same time the ICP [73].

## The self-limiting venous collapse feedback loop model

The pathogenic role of venous stenosis in the IIH/IIHWOP is debated. The sinus reopening after CSF diversion [91] or after LP with CSF withdrawal [17, 67, 92], on one hand, and the immediate and sustained efficacy on ICP showed by sinus wall stiffening with intravascular stenting [19, 71, 72], on the other, clearly indicate that CSF pressure and DSp are engaged in a positive feedback loop. Whether this loop is triggered by a pre-existing raised intracranial pressure promoting the venous collapse [68, 93] or it depends on a primary abnormal dural sinus collapsibility at CSF pressure values within the spontaneous daily fluctuations, is a matter of debate [13, 65, 94].

There is evidence of a strict coupling between ICP and DSp in subjects with IIH/IIHWOP [95] that lacks, instead, in the majority of patients with secondary forms of intracranial hypertension [96] as well as in individuals without cerebral fluid dynamics disturbances [97]. Recent evidences highlight that the ICP threshold for venous collapse in IIH patients may be close to the upper limit of the normal range [94] or within the range of the Valsalva-associated ICP fluctuations observed in pulmonary infections with protracted cough [65]. Also considering that sinus venous stenting fully normalize the ICP in most cases [71, 72], the hypothesis that a primary ICP raise leads to a secondary development of sinus stenosis is unlikely. On the contrary, the above considerations strongly suggest that IIH/IIHWOP patients harbor a degree of resistance of the sinus wall to external compression lower than expected.

We have recently proposed a pathophysiological model of IIH/IIHWOP based on the causative role of sinus stenosis.

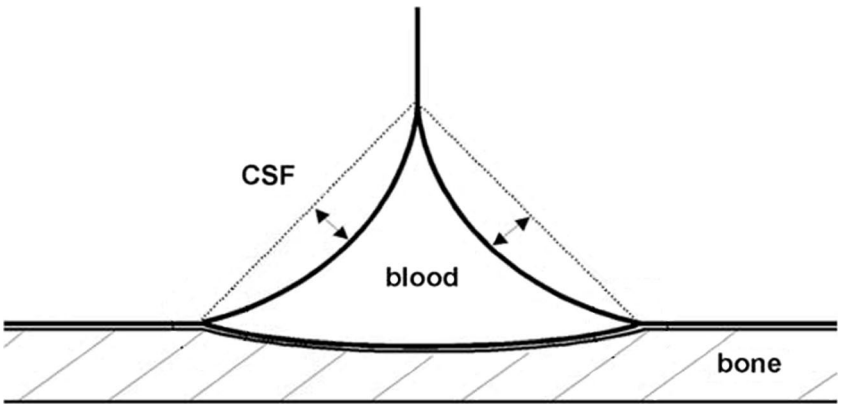


**Fig. 2** Collapsibility of dural sinus is limited by their prismatic shape, with a side attached to the bone

The model, called self-limiting venous collapse (SVC) feedback loop [13], is focused on the mutual reinforcement between the ICP, which compresses the dural sinus, and the raise of sinus pressure that in turn increases ICP.

The SVC feedback loop has three main properties:

- It is self-limiting. The loop stops once the maximum stretching of the sinus wall is reached so that the continuous CSF production may raise the ICP up to the restoring of the DSp/CSFp gradient needed to normalize the CSF excretion rate, although at higher absolute pressures. This leads to a new, relatively stable, equilibrium between the DSp and CSFp, at higher values
- It is self-sustaining. The new balance may persist even after the ceasing of the primary triggering factor, resulting in long-standing clinical syndromes [65]
- It is reversible. The new balance may revert, provided that an adequate perturbation is carried to whichever side of the loop, sinus venous stenting [19, 71, 72], on one hand, and CSF shunting [91] or even a single LP with CSF subtraction, on the other [17, 28, 67, 92]. Indeed, an acute CSF volume reduction by even a single LP may enlarge the sinus narrowing, reducing the venous hypertension and enhancing the CSF discharge with further ICP reduction. This drives a virtuous circle that, once the veins expansion is completed, may temporarily restore the physiologic DSp/CSFp balance point. The reversibility of the SCV feedback loop fully explains the long-standing remissions commonly observable after a single LP with CSF withdrawal.

## Sinus venous collapse as a second, pathological, Starling resistor

Sinus collapsibility may either result by a congenital weakness or abnormal sinus conformation and might increase over time due to the progressive plastic deformation of the sinus wall under physiologic ICP fluctuations. Sinus collapse occurs when the external CSF pressure overcomes the internal venous pressure. As such, it may be described as a second, pathological, SR placed downstream the physiological one at the bridge veins level. The distal SR replicates, and partly replaces, the functions of the first one. In fact, a significant pressure gradient can be measured across the stenosis [19, 71, 72] that consistently reverts after sinus wall stenting procedures. As in bridge vein, also into the dural sinus, the venous pressure raise upstream the collapse is proportional to the ICP increase. But here, the consequence is also the impairment of the waterfall effect which, in turn, reduces the CSF reabsorption rate through the AGs expanding the CSF volume and increasing the ICP.

Among the known SR properties, there is the self-excited oscillation of flow when the SR starts to collapse [98]. Actually, monitoring studies confirm that ICP spontaneously fluctuates in most individuals, encompassing, in IIH/IIHWOP patients, the upper limit of the normal range up to definitely pathologic values [24, 36]. Of note, a mathematical modeling study [99] has demonstrated that placing a mathematical SR at the transverse sinus level replicates the wide spontaneous ICP fluctuations documented in IIH/IIHWOP patients by ICP monitoring studies.

## CSF volume expansion reduces the cerebral compliance and anticipates the intracranial pressure increase

Cerebral compliance is the ability of the central nervous system to accept volume changes in one of its own compartments without significant increases in ICP. Cerebral compliance is limited to the first 10 ml of experimental CSF infusion [100]. For further infusions, the CSF pressure begins to raise with an increasing speed so that small increments in CSF volume result in a high ICP raise. It is therefore necessary that cerebral compliance is exhausted before ICP begins to raise. Likely, the periodic mismatch between the CSF production and excretion rates occurring during the SVC-triggered high CSF pressure waves leads to the progressive expansion of the CSF volume at the expense of more compliant intracranial compartments with compliance reduction. Actually, most of the neuroradiological signs associated to IIH such as empty sella, optic nerves, and other cranial nerves enlargement, Meckel's cave expansion [101] and external hydrocephalus [102], reflect the presence of CSF in intracranial spaces in which it is normally poorly represented or absent [103].

The increment of extraventricular CSF volume has been documented in obese IIH patients by Alperin [104] who also found that the brain compliance is generated mostly in the spinal compartment [105] and normalizes after CSF subtraction by LP [106]. At this level, large capacity intraspinal venous plexus is present (up to 800 mL) [80]. The expansion of CSF may therefore imply a correspondent decrease of the spinal venous plexus volume [107] and may initially occur without appreciable pressure changes [100]. These plexuses are devoid of valves, indicating that the blood may have to travel in both directions depending on the fluid dynamic changes promoted by physical efforts and postural changes. Spinal venous plexuses are richly anastomosed, at the bottom, with the extraspinal plexuses and abdominal veins and, at the top, with the transverse and sigmoid sinuses [79]. They represent an important route of cerebral venous outflow, especially active in standing positions [108]. Therefore, a cerebral compliance exhaustion may also imply an increased resistance to cerebral venous outflow through the spinal venous plexuses.

### May the exhaustion of cerebral compliance have a pathogenetic role in IIH/IIHWOP?

The venous pulsatility is increased in IIH and is associated with a reduced intracranial compliance that normalizes after LP [109]. A profound rearrangement of intracranial fluid dynamics, also involving an increased total arterial inflow and promptly reversed after CSF subtraction or sinus stenting, has been found in IIH [28, 81]. The normalization of the pulsatility index at the superior sagittal sinus (SSS) level after a single LP may predict a long-term benefit even in subjects not showing enlargement of sinus stenosis soon after CSF withdrawal [28]. In the study of Lazzaro et al. [109], the intracranial compliance was negatively correlated with cerebral perfusion. In addition to the mentioned hemodynamic changes, an exhausted compliance is expected to increase the amplitude of the typical spontaneous fluctuations of CSF pressure associated with IIH/IIHWOP. Thus, very likely, an almost exhausted compliance is already a pathological condition that may be symptomatic [110] despite a normal CSF pressure at rest. An isolated exhaustion of the intracranial compliance might explain the symptomatic IIHWOP cases responsive to LP [23, 25, 111] or to dural sinus stenting [112] despite moderately elevated or even normal OP.

## IIH/IIHWOP: a potentially reversible new intracranial fluids pressures balance state, at higher values

The proposed sequence of events leading to the development of IIH/IIHWOP is as follows: a low resistance of sinus wall promotes periodic SVC feedback loop-dependent CSF pressure waves, triggered by the physiologic ICP fluctuations or even self-excited → transitory mismatches between CSF production and excretion rates with CSF volume increase → progressive exhaustion of the intracranial compliance → progressive increase of amplitude, frequency, and duration of the ICP waves, with further CSF volume expansion at the expense of the craniospinal venous compartment → relatively stable, but potentially reversible, new balance state between ICP and DSp, at higher values, when the maximum venous collapse degree is reached.

In other words, idiopathic intracranial hypertension with or without papilledema, should be viewed as the direct consequence of the excessive flexibility of the dural sinus walls, in presence of predisposing factors, such as the anatomical restriction of total dural sinus cross-section, and of promoting factors, first of all obesity, a condition associated with central venous pressure raise [113] and that correlates with the increase of both, the dural sinus pressure and the trans-stenosis pressure gradient [114].

## IIHWOP in chronic migraine

The clinical presentation of IIHWOP may be limited to a mild to moderate continuous headache, fulfilling diagnostic criteria for chronic tension-type headache [115]. However, in many cases, IIHWOP presents with daily recurrences of severe migrainous pain, often with superimposed vestibular symptoms, a picture very close to CM presentation. According to the results of the first systematic study on the coexistence of IIHWOP in chronic headache patients [20], obesity and pulsatile tinnitus predicted the presence of IIHWOP while the headache profiles of IIHWOP patients did not differ from that of chronic headache patients without evidence of raised CSF pressure. Actually, IIHWOP is diagnosed in 10% [22] to 14% [21] of unselected CM series, and up to 86.4% of medically unresponsive CM patients [23, 25, 26]. IIH may occur without headache in non-migrainous individuals or in the course of a well-known migraine protective factor such as pregnancy [40]. This suggests that in non-headache prone individuals, IIHWOP may be almost asymptomatic and that CM-like clinical presentations of IIHWOP could require a migrainous predisposition. Idiopathic intracranial hypertension and CM also share some relevant risk factors such as female sex, obesity, and sleep disturbances [5], and both are associated with high sinus stenosis prevalence [13]. Topiramate, a drug with established evidence of efficacy in CM, shares with acetazolamide in the inhibition of carbonic anhydrase isoenzyme [116] and has been found as effective as acetazolamide in IIH treatment [117]. Thus, IIHWOP and chronic headaches are often comorbid; share overlapping clinical presentations, high prevalence of sinus stenosis, and risk factor profiles; and are both responsive to topiramate. Taken together, these analogies raise the question of a pathogenetic link between the two conditions and support the hypothesis that an overlooked sinus stenosis–associated IIHWOP comorbidity could represent a powerful, although modifiable, risk factor for headache progression in primary headache prone individuals [48]. Robust available data strongly supports this hypothesis. Actually, bilateral sinus stenosis can be found in 5 to 23% of the general population [49, 118] but reached 48% in a chronic headache series in which MR venography was performed just before 1-h ICP monitoring evaluation [24]. Notably, an ICP > 200 $mmH_2O$ was found in 91.6% of bilateral sinus stenosis carriers and none in patients showing unilateral stenosis or normal MR venography. In a recent study [25], we have found an OP > 200 $mmH_2O$ in 86.4% of 44 CM subjects with prospectively assessed unresponsiveness to treatments, and that a single LP with CSF subtraction was followed by the immediate resolution of symptoms in 77.3% and maintained in 54.6% at 2 months and in 38.6% 4 months after the procedure. These findings have been included in a recent authoritative review focused on the risk factors for migraine progression [119]. The causative role of the IIHWOP/CM comorbidity highlighted by

our study has recently been confirmed by a second independent study demonstrating that in CM subjects showing an OP > 200 mm$H_2O$ a single LP with CSF removal may induce the immediate remission of CM symptoms, maintained up to 6 months in a subset of patients [23]. Accordingly, IIHWOP may be causatively involved in the progression of migraine at least in migraine-prone individuals.

### Mechanisms linking IIHWOP and CM

The extraordinary comorbidity linking IIH/IIHWOP and CM [20–22] could be secondary to two different mechanisms, not mutually exclusive. The first is represented by the cerebral perfusion increase associated with migraine attacks which could lead to transient cerebral venous insufficiency in subjects with anatomical narrowing of the total venous cross-section [89]. The second may refer to the sensitization of central pain pathways, generated by the activation of a trigeminovascular nociceptive firing from the dural sinuses and bridge veins. The dural sinuses are among the most pain-sensitive structures of the whole vascular tree and of the meninges [120, 121]. Being richly innervated by peptidergic trigeminovascular terminations from the I branch [122], dural sinus stimulation produces changes in brain blood flow and in neuropeptide levels similar to those seen in humans during migraine [121]. In a very recent immunohistochemical study on SSS of cadaver [123], it was possible to demonstrate that the trigeminal terminals are widespread throughout the SSS and at the BV openings and contain large amounts of calcitonin gene-related peptide (CGRP) and other neuropeptides like substance P (SP), neuropeptide Y (NPY), and vasoactive intestinal polypeptide (VIP). Moreover, "Ruffini like" mechanoreceptors have been found mainly at the level of the BV openings, where also actin filament could be identified. On the basis of these observations, the authors suggest that trigeminovascular nociceptive innervation of SSS and of bridge veins may have a role in cerebral venous pressure monitoring and are involved in the regulation of the cortical veins discharge into SSS. It can be speculated that, in sinus stenosis–associated IIHWOP patients, the congestion of the dural sinuses may lead to a sub-continuous, CGRP-dependent, trigeminovascular nociceptive firing, responsible for the sensitization of central pain pathways and for the progression of migraine towards a chronic pattern [48]. This raises the hypothesis that the venous side of brain perfusion could represent a major source of CGRP with possible relevance in migraine mechanisms.

As said, obesity may have a direct causative effect on IIH/IIHWOP [114]. Besides, the possible much higher prevalence of IIHWOP [48], the almost mandatory diagnostic role currently attributed to papilledema, the unusually high migraine prevalence in IIH (63.2%) [124], and the observation that IIH presentation with headache may require a migrainous background (a condition four times more frequent in female sex of childbearing age) may explain the rarity with which IIH is diagnosed and its much higher prevalence among young obese women.

## Conclusions

A number of crucial assumptions on IIH with or without papilledema might be revised. Available evidences suggest that a reduced rigidity of dural sinuses is causatively involved in IIH/IIHWOP pathogenesis, provided that a sinus collapse may start at pressure values encompassed into the large physiological fluctuations of ICP occurring in daily life; a reduction of the cerebral compliance anticipates the intracranial pressure raise and may be pathologic itself; the papilledema remains a very specific IIH sign although its absence does not make a definite diagnosis less probable; and the prevalence of IIHWOP is much higher than believed but this condition is frequently overlooked or misdiagnosed at present, mainly as chronic migraine. The pathogenetic link underlying the high comorbidity between IIHWOP and CM relay on the abundant peptidergic trigeminovascular innervation of dural sinuses, acting as an intracranial venous pressure sensor and leading to the sensitization of central pain pathways. Dural sinuses and bridge veins represent a major source of CGRP which could explain the emerging causative link between IIHWOP and CM. The control of ICP may represent a new promising therapeutic target in CM.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical standards** This article does not contain any study with human subjects performed by any of the authors.

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