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The State of Spontaneous Intracranial Hypotension in 2020: A Mini-Review

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The history of intracranial hypotension dates back to the early 1900's, when trephined patients with depressed scars were observed to show decreased pressures via lumbar puncture manometry[1]. The first formal description of the syndrome is commonly attributed to Leriche, who in 1920 interpreted symptoms of severe headache, nausea and vomiting, hyperthermia and coma in patients with closed skull fractures as secondary to hypotension due to loss of fluid through the fractures[2]. Following this period, recognition of intracranial hypotension and its associations with CSF leak secondary to trauma, overshunting, lumbar puncture and surgery gradually increased[3,4]. The primary form, now termed idiopathic or spontaneous intracranial hypotension (SIH), was also acknowledged. More recently, the etiology for SIH has been attributed to CSF leaks due to osteodiscogenic microspurs, rupture of spinal nerve root diverticula, or, more controversially, CSF-venous fistulae[5,6]. Its association with various connective tissue disorders including Marfan syndrome and Ehlers-Danlos syndrome are also recognized[7]. Although much of the discussion in this mini-review also applies to secondary intracranial hypotension, special emphasis will be made on the primary form due to its inherently increased challenge in recognition, diagnosis and treatment.

Interestingly, the concepts integral to understanding the pathophysiology of intracranial hypotension were described well before the acknowledgement of the actual disease. The classic Monroe-Kelly doctrine was established in the late 1700s to early 1800s[8,9], describing a constant volume of blood, brain and CSF within the rigid skull and that change in one of these compartments leads to the compensatory shift in another in order to maintain intracranial pressure. When autoregulatory mechanisms fail, intracranial pressure rises or falls depending on the volume gained or lost in one or more compartments[10]. In the case of intracranial hypotension, CSF loss results in compensation by increasing the volume of the venous compartment, given its increased compliance, leading to venous engorgement[11]. Secondly, the loss of buoyancy forces provided by CSF results in downward slumping and herniation of brain tissue[12]. These effects are exacerbated by gravity when the patient is upright via CSF and venous overdrainage[11] and provide the basis for understanding the clinical manifestations of the disease and imaging findings.

The most common presenting symptom in SIH is orthostatic headache, thought to result from traction on meninges, sensory nerves and bridging veins[13]. Venous distension resulting in either direct stimulation or secondary subdural hematomas also likely contributes to symptomatology[14]. A curious phenomenon that cranial sites of CSF leak

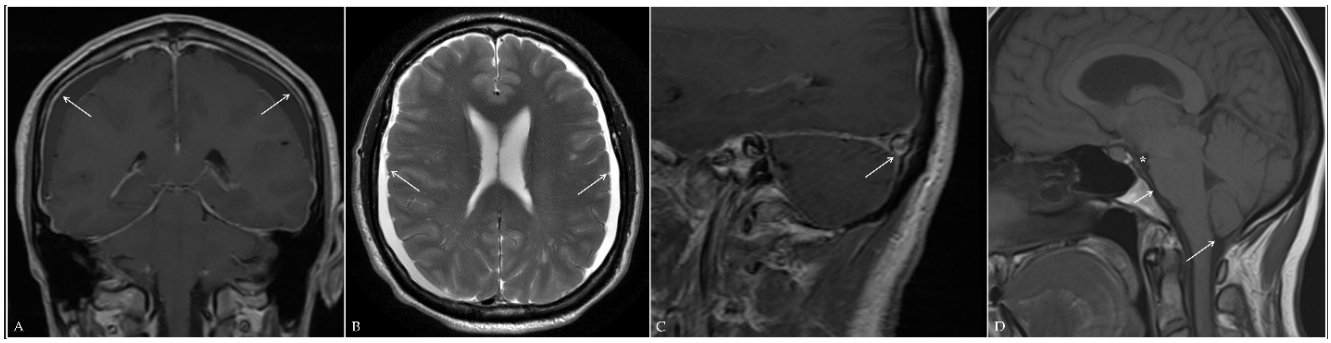

Figure 1: Spontaneous intracranial hypotension findings on brain MRI include pachymeningeal thickening and enhancement (A), bilateral subdural collections (B), venous engorgement, manifested by the venous distension sign (C), and brainstem slumping (D), in this case illustrated with effacement of the prepontine cistern (*), flattening of the anterior surface of the pons (short arrow), and tonsillar herniation (long arrow).

rarely cause orthostatic headache[15] led to the hypothesis that alterations in the distribution of craniospinal elasticity due to spinal sites of CSF leakage are an additional cause of headache[16]. Other common symptoms of SIH including nausea, vomiting and neck pain as well as more significant symptoms of vertigo, diplopia, tinnitus, ataxia and coma are attributed to downward traction and compression of cranial nerves, brainstem and cerebellum[17]. Another potential serious complication is cerebral venous thrombosis, with an estimated incidence of 2%[18]. The mechanism is thought to be a combination of venous dilation-related stasis, mechanical vascular distortion and increased blood viscosity due to CSF depletion and subsequent reduced resorption[18]. Finally, superficial siderosis has a rare but well-established association with spontaneous intracranial hypotension with a spinal CSF leak seen in approximately one third of patients[19]. The pathophysiology is attributed to chronic recurrent bleeding of superior cerebellar bridging veins.

The difficulty in diagnosing SIH has been well recognized dating back to the earliest texts and unfortunately, remains true to this day. Due to its non-specific presenting symptoms and signs, the cause is often misattributed to other etiologies such as migraine, meningitis and psychiatric disorders[20]. The delay in diagnosis can range between days to years with mean 13 months[20]. Given the potential for grave consequences in missing this entity, knowledge in its presentation and workup is paramount. The diagnosis of SIH, as outlined in the International Classification of Headache Disorders, 3rd edition, is based on the combination of headache in temporal association with either direct measurement of low CSF pressures (< 6 cm CSF) or typical imaging features directly or indirectly suggesting a CSF leak, in the absence of a procedure or trauma known to be able to cause CSF leakage[21]. Unfortunately, spinal manometric readings can be normal in a large proportion of affected patients[22]. In the past, the diagnosis was established with intraoperative exploration, trephination and intraventricular puncture[1]. Fortunately, given the advancement and increased availability of medical imaging, non-invasive MR imaging is now the first line test for assessment of patients presenting with typical and atypical symptoms of intracranial hypotension.

Several direct and indirect MRI findings have been described in intracranial hypotension. In cases with high clinical or brain MRI suspicion for SIH, a spinal MRI examination is generally recommended to look for a spinal CSF collection, which can be directly visualized in approximately two-thirds of cases[23], although the exact site of leakage is often occult without dynamic imaging. Recently, MR myelography was shown to be nonsuperior to conventional MRI with heavily T2-weighted fat-saturated images[23]. In contrast, non-specific clinical presentations are generally assessed initially with brain MRI and the diagnosis rests on making secondary observations. The described classical findings include subdural collections (often bilateral), pachymeningeal thickening or enhancement (if a gadolinium-based contrast agent is given), venous engorgement and brainstem slumping[24-27] (Figure 1). Revisiting the Monroe-Kelly doctrine provides insight into the mechanisms by which these findings present. Venous engorgement is directly manifested as distension of dural venous sinuses and the most sensitive MRI sign of pachymeningeal thickening (up to 80%), which represents dilation of tiny dural venules. The downward shift of intracranial structures due to loss of buoyancy forces is manifested on sagittal MR images as brainstem slumping and tonsillar herniation. Both venous overdistension of and traction on bridging subdural veins predisposes to rupture and consequent subdural hematomas[28].

While the presence of multiple classical findings is sufficient in diagnosing intracranial hypotension, in many cases, a limited number of findings may be present. Individually, these classical findings can be non-specific, such as pachymeningeal enhancement, and subjective with poor inter-observer reliability, such as the brainstem

slumping[29]. Due to these factors, much research has been done to find objective imaging markers for intracranial hypotension. Venous engorgement has been traditionally assessed by the subjective presence of a prominent epidural venous plexus at the craniocervical junction and enlargement of the pituitary gland[29]. An objective assessment for venous engorgement, termed the "venous distension sign", was found to be 94% sensitive and specific for the diagnosis of intracranial hypotension[30]. Brainstem slumping has also been previously assessed by subjective markers, including the effacement of basal cisterns, descent of the corpus callosum splenium, and flattening of the anterior surface of the pons[25,26,31]. Objective markers evaluating for loss of CSF space with resultant anatomic shift include the mammilopontine distance and pontomesencephalic angle as well as various measurements between suprasellar structures (mammillary bodies, optic chiasm, infundibular recess, etc.) and reference lines (Chamberlain's line, tuberculum sellae-venous confluence line, etc.)[29,31-32]. Recently, the interpeduncular angle has been found to be a reliable objective marker that has good sensitivity (80%) and specificity (97%) for the diagnosis of intracranial hypotension (Figure 2)[33]. Different from previous measurements, it is assessed on a standard axial T2-weighted MRI sequence and requires no additional reference line, likely contributing to its reproducibility. Various grading schemes incorporating subjective and objective imaging markers have also been proposed[32,34]. These, to date, have not been adopted into routine clinical practice.

Initial treatment for SIH aims at symptomatic control with rest, rehydration and analgesics[35]. High oral caffeine intake and theophylline have been suggested, thought to improve low intracranial pressure headaches through their well-established association with cerebral vasoconstriction[36]. The use of pelvic binders is theorized to elevate intracranial pressures through compression of pelvic veins with increased back pressure into the epidural venous plexuses[37]. Despite the favorable response some patients with mild symptoms experience with conservative management, evidence for these measures remains largely anecdotal and many patients require more invasive therapy, the mainstay of which being epidural blood patch (EBP). In this procedure, approximately 10-30 mL of autologous blood is injected into the epidural space to tamponade or "plug" the dural tear, either blindly or specifically targeting the level at which a CSF leak is identified. Overall success to EBP has been favourable, with response up to 77% of cases, although up to 50% of patients require multiple treatments (up to 6) [38-40], the timing of which is dictated by symptom recurrence. Not surprisingly, a targeted approach has appeared to be more effective than a nonselective injection, although data has been limited to small retrospective studies[41,42]. In an attempt to improve non-targeted therapy in cases where the site of CSF leakage cannot be identified, recent procedural modifications include multi-level large volume (average 50 mL) and even ultra-large volume (up to 120 mL) injections[43,44]. The success of these are again limited to case reports. An alternative sealant for the dural rent is fibrin glue, which has also been successful in a number of case reports[45,46]. Surgical exploration and repair is reserved for patients refractory to conservative management and percutaneous treatments. Ideally, a definite or suspicious site of CSF leak is identified preoperatively. Intra-operative interventions include dural suturing, epidural packing and ligation of meningeal diverticula[5,47]. Rarely, continuous intrathecal saline infusion to restore CSF volume may be necessary in severe or complex cases such as stuporous or comatose patients with impending or existing herniation[48,49].

Despite a century of recognition, SIH remains an elusive clinical diagnosis with serious morbidity and potential mortality. The pathogenesis for the disease stems from a CSF leak resulting in intracranial changes governed by the Monroe-Kelly doctrine. Although the name for the disease stems from its historical origins, some authors favour the term "cerebrospinal fluid hypovolemia syndrome" given that CSF pressures are often normal and that it is primarily

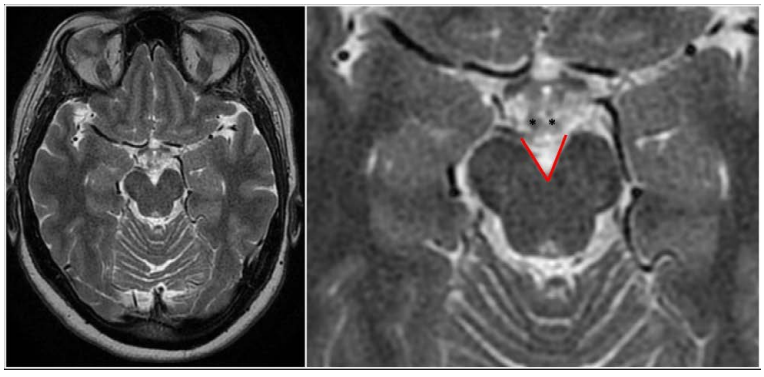

Figure 2: The interpeduncular angle is the angle formed between the posterior half of the cerebral peduncles, measured on an axial T2-weighted MR image at the level of the mammary bodies (*) or the slice immediately below, whichever yields a lesser value.

the loss of buoyancy forces due to volume depletion that results in the clinical presentation[50,51]. We agree that the disease name should reflect the pathogenesis but also recognize the importance of consistency in literature. Most importantly, more accurate nomenclature will arise through greater understanding of etiology, ideally with subsequent improvement in diagnosis accuracy and efficiency and treatment efficacy.

Conflict of interest

The authors declare no conflict of interest.

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