Chapter

The Cerebral Venous System: New Pathophysiological Theories and Diseases Related to Veins Occlusion

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Abstract

Cerebral physiology and pathology are still frequently missing a comprehensive explanation and a complete description, but new data and hypothesis are emerging on a daily basis. Particularly, comprehension of the cerebral venous system's functions and functioning has undergone through the last decades a deep and extended change. Depiction of the perivascular spaces and the mechanisms of glymphatic system has given light about venous system pivotal role in the genesis of different pathologies such as multiple sclerosis, hydrocephalus, cerebral hemorrhages, and strokes. After a key point discussion about embryology, physiology, and anatomy of the cerebral venous system, an overview is provided on the main pathologies, both well-known and newly described ones, in which cerebral veins act a major pathogenic role.

Keywords: cerebral venous system, glymphatic, multiple sclerosis, cerebral vein thrombosis, eagle jugular syndrome, JEDI syndrome

1. Introduction

The cerebral venous system (CVS) is a wide, dynamic, and connected net of vessels developing from the encephalic parenchyma to the internal jugular veins (IJVs). As other venous system, it has three main functions: to drain blood and catabolites from the brain, to help maintaining thermic homeostasis and to refill the right-sided heart [1]. Differently from other organs, instead, intracranial veins share unique physiological features and functions. Traditionally, comprehension of CVS has been limited to descriptive anatomy and a few ranges of physiological principles.

New emerging evidences in the last years are depicting a more complex scenario, in which CVS has a pivotal role in starting and sustaining various pathological processes, from multiple sclerosis to cerebral hemorrhages, hydrocephalus, and strokes.

2. A look into the normal basic anatomy, physiology, and new theories about the glymphatic system

2.1 Developmental embryology

Primitive CVS starts differentiating from primary meninx mesenchyme as a continuous endothelial plexus connecting the dural (*ectomeninx*, the outer portion of primary meninx) and the pia (*endomeninx*, the inner portion) layers. In the first trimester, around the 12th week, a progressive coalescence and resorption of vessels reduces the dura-pial anastomosis to 10–18 bridging veins with specific anatomical features. On the other side, the ectomeninx form the dural folds (falx and tentorium), containing the progressively forming dural sinuses. This early and definitive separation between the parenchymal and dural CVS gives the basis for the blood-brain barrier (BBB) formation [2].

Classically, first clearly identifiable parenchymal vessels are the prootic, the anterior cerebral, and the capitis lateralis and medialis veins [3].

From the 4th to the 5th months, the cortical veins net rapidly grows to sustain the hemisphere fast development. Consequently, the dural sinuses size increases with multiple series of anatomical variations and modifications from week to week. The transverse sinus balloons in response to this increasing amount of blood and to the relatively narrow diameters of jugular vein, with formation and enlargement of multiple emissary vessels for extracranial drainage to the foramen magnum and vertebral plexuses [4]. At the 35-mm stage of the embryo, drainage from the transverse sinus to the IJV can be detected [4].

After birth to the 1st year, the jugular bulb increases in size thanks to the physiological modifications of postnatal circulation, and the drainage through the emissary veins reduces its flow.

2.2 Basic anatomy

Throughout the uterine life, CVS anatomy is dynamically changing in response to the morphometric and hemodynamic adaptations of the growing organism. Progressively, from the chaotic but not homogenous primitive plexus, certain preferential routes are selected on the basis of rheologic flow parameters, while others disappear. The most suitable venous patterns are fixed, independently from our anatomical classifications, similarly to what happens for arteries but with far more variability.

In the ideal description, CVS can be distinguished in parenchymal and dural circulation. It is important to notice that intracranial veins are lacking of intraluminal valves, differently from other veins in the systemic circulation.

The deep parenchymal circulation drains blood from the deep white matter of the cerebral hemisphere, the basal ganglia, and the mesencephalon.

Dural CVS is comprised into the dural sinuses, spaces originated from the splitting of the dura derived from the ectomeninx and covered by endothelium, as above specified.

2.3 Physiology

Arterial blood enters the brain through the anterior circulation, via the carotid arteries, and the posterior circulation, via the vertebral arteries. Also venous blood,

or at least the major part of it, exits the brain through an anterior circulation, via the IJVs, and a posterior one, via the vertebral plexuses. Once passed the osteo-dural ring of their respective entry points inside the skull, circulatory physiology of these vessels drastically changes, given the unique physical conditions that are present in the intracranial space.

Although an exhaustive dissertation on cerebrovascular physiology is not in the focus of the present chapter; to understand CVS physiology, few mechanical, hydrostatic, and anatomical principles have to be clarified.

The skull (bone and dura together) is basically a rigid, non-expandable container, totally filled with uncompressible materials: brain parenchyma, blood and cerebrospinal fluid (CSF).

Around 1764, Alexander Monro, second of his name, published *Observations on the Structure and Functions of the Nervous System* [5], in which he theorized his famous principle: "*For, as the substance of the brain, like that of the other solids of our body, is nearly incompressible, the quantity of blood within the head must be the same, or very nearly the same, at all times, whether in health or disease, in life or after death*" [5]. Few years later, George Kellie, one of his students, and John Abercrombie, a pathologist, confirmed his findings and endorsed his theory.

In 1926, Harvey Cushing published "*Studies in intracranial physiology & surgery; the third circulation, the hypophysics, the gliomas*" [6] in which he summarized previous knowledge about intracranial physiology. One of the results of this milestone book was the easy-to-remember equation about Monro-Kellie principle:

$$\text{Brain volume} + \text{CSF} + \text{blood } vol = \text{K} \tag{1}$$

This is an effective way to summarize the concept, but this formulation lacks the fundamental pulsating nature of cerebral flow. Blood enters the brain pulsating in the arteries; then the mechanical wave of pulsation is transmitted anisotropically through the parenchyma and CSF (fluids with different elastic properties). This wave propagation deeply affects CVS physiology: if blood enters the skull pulsating into the arteries, also it leaves from the vein pulsating.

In this balance of pressure between inflow and outflow, bridging veins have a pivotal role.

A bridging vein is defined as a cortical vessel that drains venous blood from the parenchyma to the sinuses, detaching from the cortex and crossing the subarachnoidal CSF filled and the subdural space. It has thin walls (subdural portion 10–600 μm; subarachnoid space of 50–200 μm) with loose collagen network and no muscular fibers [7]. So constituted, it acts as a perfect Starling resistor: a collapsible tube, filled with a fluid exerting pressure (P1, blood venous pressure), inside a space filled with another fluid exerting a different pressure (P2, CSF/intracranial pressure). To maintain a flow inside the tube, it is necessary that P1 > P2.

While entering, or exiting, the cerebral cortex, the superficial arteries and veins in the subarachnoid space are ensheathed in a leptomeningeal coverage, filled with CSF in a double triangle shape. These invaginations are known as Virchow-Robin spaces in their original description [8] and previously taught to be a virtual space, enlarged only in pathological processes. Further studies during the last decades reassessed the importance of these channels and prosecuted their anatomical micro description, thus renaming it perivascular spaces (PVSs).

Deeper into the parenchyma, PVS surrounds the penetrating arteries and capillaries, and it includes a real space that exists between the endothelial basement

membrane (aka *basal lamina*), a thin lamina of extracellular matrix components, and *glia limitans*, defined as the barrier formed by perivascular end feet of astrocytes, rich in channel proteins as aquaporin-4 (AQP4) [9]. At the same time, vascular endothelial cells are linked each other by tight junctions, one of the main components of blood-brain barrier (BBB) that restrict macromolecules diffusion inside the parenchyma.

This anatomical description is better defined for the arterial side of cerebral circulation, while venous PVS has not been thoroughly characterized yet.

Intracranial fluids can be divided in intracellular fluid (ICF, 60–70%), interstitial or extracellular fluid (ISF 20% 280–300 mL), blood (10%), and CSF (10% 140–150 mL). Passage of ions, solutes, and molecules between one compartment and the others is precisely regulated to maintain the different chemical composition necessary to their respective physiological role (e.g. plasma contains approximately 270 times more proteins than ISF) [10].

2.4 Glymphatic system

From 2012, a series of experiment on animals and mathematical models led to the discovery and description of the so-called "*glymphatic system*" [11]. This physiological mechanism is taught to act as a cerebral lymphatic system, seen that cerebral tissues lacks a properly formed net of lymphatic vessels and nodes. It is proposed that water from the CSF enters the interstitium by the PVS of the penetrating vessels and capillaries, passing through the filtering glia limitans. Even if the fluid production per capillaries may be too little to be detectable, the total volume of fluid generated by the whole capillary endothelium (an estimated a 20 m^2 surface [9]) is quite considerable. Once interstitial, this water convectively flushes solutes and waste products, such as amyloid β oligomers, into the paravenous CSF space to be discharged.

The first evidence of an intraparenchymal bulk flow along PVS was provided by Cserr [12] in 1974 by following injected tracers.

Fluid exchanges between venular lumen and paravascular space depend primarily on transmural pressure (TMP), a fundamental hemodynamic parameter. Considering the venous wall as the exchange border for fluids, TMP is a differential pressure between internal (intravenous) pressure (IP) and external (paravascular) pressure (EP). EP is represented by the oncotic pressure of the interstitium plus the intracranial pressure (ICP). IP is the sum of blood pressure and the relative venous oncotic pressure. In turn, each of these parameters depends on several others. Of main interest is that venous pressure of parenchymal vessels depends on bridging veins (Starling resistors) function. To sustain a reabsorption flow from the parenchyma to the CVS, it is necessary that IP is lower than EP.

So, in this paradigm, a dynamic balance between CSF, ICF, ISF, and blood is continuously rearranged throughout the entire vascular, arachnoidal, and ependymal surface to maintain the physiological functions of the estimated 16–30 billion neurons of the brain.

Main driving force of this interstitial convective process is the arterial pulsation of the penetrating arteries, moving actively the CSF along the PVS [9]. Alongside, the periodical variation in ICP is generated by breathing (and similar activities that modify intrathoracic pressure) and vasomotor variations in the vascular net.

Glymphatic system function, defined as the capability of flushes toxic solutes away from the parenchyma, normally decline with aging, both in animals and humans. Proposed mechanism is a reduced CSF interstitial influx secondary to decreased pulsatility of sclerotic arteries, impaired CSF production, and reduced AQP4 expression on astrocytes end feet[9]. Hypertension and diabetes mellitus type 2 have also

been associated with a decreased glymphatic function. Similar observations have been made in cases of stroke, subarachnoid hemorrhage, traumatic brain injury, and demyelination of various origins.

3. Cerebral vein thrombosis: causes, diagnosis, and treatment

3.1 Clinical presentation

Cerebral vein thrombosis is defined as the presence, in both the cortical vessels and the dural sinuses, of clotted blood impairing physiological flow.

CVT is an uncommon form of stroke (0.5–1% of total), usually affecting young individuals with several associated risk factors (mainly related to Virchow's triad of blood stasis):

- Thrombophilia
- Inflammatory bowel disease
- **Pregnancy** (but als **postpartum** period)
- Dehydration
- Oral contraceptives
- Substance abuse
- **Rheumatologic disorders** (as systemic lupus erythematosus, Behçet disease, sarcoidosis and antiphospholipid and anticardiolipin antibodies)
- **Head trauma** [13].

Other more specific associations are made with:

- **Parameningeal infections** (ear, sinus, mouth, face, and neck)
- Complication of epidural blood patch
- Spontaneous intracranial hypotension
- Lumbar puncture
- **Cancer** (particularly in patients with hematologic malignancies)
- **SARS-CoV2 infection (COVID-19)** [14]
- **Climatic conditions** (particularly high ambient temperatures) [15].

An underestimated risk factor for CVT is a JV thrombosis that propagates cranially, often because of the presence of medical dispositive [13].

Exact epidemiology of CVT is unknown because clinical features are quite variable, and for this reason, cases should be classified differently [16].

Recently, cerebral venous sinus thrombosis in association with COVID-19 has been described, both as a first clinical presentation or a subsequent complication [17].

Clinical findings are related to intracranial hypertension, related to impaired venous drainage, and/or to focal brain injury from venous ischemia or hemorrhage. Obviously, clinical manifestations of CVT also depend on the location of the thrombosis.

Most frequent symptoms are

- **Headache** (90% of patients): typically described as diffuse and often progressive over days to weeks. Less frequently, it may present with thunderclap headache, similar to a subarachnoid hemorrhage, or a migraines-like headache. Up to 25% of patients with CVT only present with headache [16].

- **Seizures** (40% of patients): first, focal, or generalized seizures are frequent.

- **Papilledema or diplopia** (caused by sixth nerve palsy).

- **Neurological signs and deficits**: most common are hemiparesis and aphasia.

- **Scalp edema and dilated scalp veins** may be seen on examination.

When CVT is secondary to regional infection, signs and symptom of the primary cause can be detected: toothache and odontogenic abscess; ear discharge; pain in the ear, face, or mastoid region.

3.2 Laboratory exams

In patients with suspected CVT routine, laboratory essay including complete blood count, chemistry panel, prothrombin time, and activated partial thromboplastin time should be performed [9] in order to identify pro-coagulative systemic status. D-dimer assessment makes sense in presence of low pretest probability of CVT to exclude the diagnosis, similarly to pulmonary embolism. Lumbar puncture is characterized by a high opening pressure (80% of cases) but has limited diagnostic value. It is not routinely indicated unless CNS infection is suspected.

3.3 Red flags to avoid misdiagnosis

Thirty to forty percent of patients with CVT present with an intracranial hemorrhage [18]. Progressively increasing headache over days and alterations in laboratory exams with evidence of hypercoagulability should prompt further radiological assessment for evaluating CVT. Also, at the CT exam, an ischemic/hemorragic lesion that crosses normal arterial boundaries, deep bilateral, or in close proximity to a venous sinus is suggestive of CVT.

Patients complaining of isolated headache and signs or symptoms of intracranial hypertension (papilledema or sixth nerve palsies) should be evaluated for CVT. The correct differential diagnosis between idiopathic intracranial hypertension (IIH) and CVT has therapeutic and prognostic importance. In both cases, however, clinical manifestations are related to the impaired venous outflow function, with subsequent increasing of the ISF.

3.4 Radiological diagnosis

3.4.1 CT scan

In a contest of a CVT suspect case, CT without contrast may demonstrate some characteristic features, but an exact diagnosis is made complex by the intrinsic anatomic variability of the venous sinuses and cortical veins. In fact, only in 30% of CVT cases, CT scan shows some abnormalities [19].

The fundamental sign of acute CVT on a CT (without contrast) is a homogenous hyperdensity of a cortical vein or sinus. Another typical sign of the superior sagittal sinus thrombosis (posterior portion) is the filled delta sign, a dense triangle in the context of the sinus.

Only 0.5–0.8% of patients with CVT showed some signs of subarachnoid hemorrhage, often in atypical position.

The contrast-enhancing CT scan could add some clues, such as the classic "empty delta" sign: an enhancement of the dural border of the sinus with a filling defect within it due to the thrombus in a triangular shape.

This is not a precocious finding, but usually lasts for several weeks after the acute phase.

On the other hand, CT venography is much more useful in chronic follow-up because the occluded sinus cavity shows a variable density. The presence of cortical bone close to the dural sinus can produce interfering artifacts during the visualization of the enhanced dural sinus.

3.4.2 Magnetic resonance imaging

Classically inside the normal sinus, there is a flow void signal due to the venous stream continuously moving. Early signs of CVT can be visualized as *absence* of this flow void with T2 hypointensity or a central iso-hypodense lesion with surrounding enhancement.

Meanwhile, an acute thrombus, not fully formed yet, may appear as a hypointense signal, similar to the normal flow void.

Other signs include cerebral swelling, edema, and/or hemorrhage. Diffusion-weighted imaging (DWI) sequences show hyperintense signal, meaning a reduced blood flow, with a prognostic significance: brightening sinus on DWI predict low chances of recanalization.

Magnetic resonance imaging (MRI) is particularly helpful in defining the nature and extension of parenchymal lesions, causes, or consequences of the CVT: focal edema, infarction, and infectious processes.

MRI venography is the most common CVT diagnostic technique with the use of two-dimensional time-of-flight (TOF) sequences because of its excellent sensitivity to slow flow inside the sinus.

3.4.3 Cerebral angiography

Venous phase of cerebral angiography (4–8 s from the injections) typically, and directly, shows a filling defect in the occluded lumen. Other signs are venous congestion with dilated cortical, scalp, or facial veins, enlargement of collateral drainage, and venous flow reversal.

Although it is an invasive procedure, cerebral angiography (or venography) could help to solve undefined situations due to anatomic variations such as sinus atresia/hypoplasia, asymmetrical drainage, and normal sinus filling defects caused by arachnoid granulations or septa.

3.5 Treatment

Most used therapeutic approach is based on blood anticoagulation, which aims to prevent thrombus growth, avoids development of pulmonary embolism, and promotes sinus recanalization. Different drugs and different strategies are present in literature [16], with the use of unfractionated heparin (UFH), antivitamin K molecules, low-molecular-weight heparin (LMWH), and low-dose unfractionated heparin. An effective treatment is complicated by the presence of intracranial hemorrhage or cerebral infarction at the time of the diagnosis, given the increased risk of worsening the bleeding.

The available data from RCT comparing clinical/radiological outcomes and bleeding complications support a safe and effective role for anticoagulation in the treatment of CVT, even if intracranial bleeding is present [16]. There are no data that suggest the preferential use of UFH or LMWH in CVT patients. Some data suggest that, if pulmonary embolism or deep vein thrombosis is present, LMWH have to be preferred [20].

In case of secondary CVT (infection, trauma, and other transient causes) vitamin-k antagonist should be continued for 6 months after the removal of the causative factor [16].

Otherwise, in case of primary CVT, vitamin-k antagonist should be continued for 6–12 months and further coagulative assessment should be carried on [16].

Other therapeutic options include

- **Fibrinolytic therapy**: preferentially used when clinical worsening is present even if anticoagulation is well conducted, or in case of intracranial hypertension not responsive to other treatments. There are few evidences that fibrinolysis increase the recanalization rate of the occluded sinuses [18]. It could be delivered as systemic therapy or by direct sinus catheterization (thrombolysis), in this case a mechanical thrombectomy can be associated.

- **Surgery**: decompressive craniectomy or hematoma evacuation may be a necessary life-saving measure if a significant increase in intracranial pressure progresses despite conservative treatment.

- **Antibiotics**: mandatory if CVT is secondary to propagating infections, when possible, in association with drainage of purulent sources (subdural empyemas or purulent collections within the paranasal sinuses).

- **Antiepileptic drugs**: indicated only in case of seizures (even one), without preferred molecules, to reduce the risk of anoxic damage.

- **Corticosteroid**: even if useful to reduce vasogenic edema, steroid could alter blood homeostasis and enhance clot formation. There are evidences that steroid increase the overall risk of death or dependence with steroid treatment at 6 months in CVT patients [21].

4. Jugular vein stenosis

Cerebrospinal venous insufficiency is an emerging nosological entity collecting different conditions that shares an impaired venous outflow from the brain to the heart. Multiple central nervous system disorders, such as idiopathic intracranial hypertension (IIH), Ménière disease, transient monocular blindness, and Alzheimer's disease, have already been reported to be associated with internal jugular vein (IJV) stenosis [22, 23]. Nowadays, different branches of medical sciences are directing their attention to the delicate balance between cerebral inflow and outflow in order to better understand CVS physiology and its correlation with several disorders. As a mechanical system, a CVS flow obstruction from any causes at any level lead to an increased pressure transmitted upward. This means an increased capillary pressure, thus an increased TMP and finally a decreased glymphatic paravascular ISF flushing and reabsorption into the CVS. Proceeding from the parenchyma to the major vessels, venous convergence reduces the possibility of alternatively restoring a fully functioning flow. Once in the IJV, collateral drainages are few and of limited caliber. So, at this level, any stenosis (intraluminal, parietal, or extraluminal) produce effects diffused at the entire CVS and to the parenchyma. In the mathematical Gadda-Ursino hemodynamic model of CVS outflow, a jugular stenosis is a significant parameter in sinus pressure regulation [24].

Over the last years, several new pathologies have been described related to IJV obstruction, and old ones received new interpretations.

4.1 JEDI syndrome

Usually, patients suffering from IIH are women with elevated BMI and normal to slit cerebral ventricles [25]. Meanwhile, IIH has a strong relation with impaired CVS outflow caused by increased thoracic-abdominal or dural sinuses pressure (obesity, CVT, and superior vena cava syndrome). On the other hand, acutely dilated ventricles are related to high-pressure hydrocephalus caused by cerebrovascular pathology (infection, trauma, and hemorrhage).

Recently, an anomalous IIH case with dilated ventricle (Evans index 0.36) has been described in a woman with normal BMI complaining of headache, visual loss (Frisen grade 4 papilledema), and pulsating tinnitus. Neuroimaging did not reveal any causes of hydrocephalus from intracranial lesions, while a fluorodeoxyglucose (FDG) positron emission tomography (PET) described a diffuse hypometabolic cerebral state.

At B-mode echography of extracranial IJV, a bilateral external compression from omohyoid muscle was demonstrated, hemodynamically corresponding to blocked venous flow with scarce collateral compensation.

The patient underwent surgical bilateral resection of omohyoid muscle with ICP invasive monitoring. After transection of the muscles, a sudden drop in ICP and normalization of ICP wave were observed.

Headache and tinnitus disappeared after surgery, and papilledema progressively improved with visual acuity restoration. Serial (24 months' follow-up) MRI documented regression of Evans index and FDG-PET showed improvement of brain metabolism.

These peculiar cases led to the description of a new clinical entity, a form of hydrocephalus that does not require CSF shunt procedures. This syndrome has been called JEDI (jugular entrapment dilated ventricles intracranial hypertension) syndrome [26].

While an extracranial obstacle to CVS is coherent with intracranial hypertension for the aforementioned principles, it is still unclear what caused ventricles dilatation in this case. More studies are needed to fully comprehend the relation between IJV obstruction, IIH, and hydrocephalus.

4.2 Eagle jugular syndrome

In 1937, the American otolaryngologist Dr. Eagle was the first to describe a clinical syndrome caused by an elongated styloid process [27]. The stylohyoid complex is composed of styloid process, stylohyoid ligament, and the lesser horn of the hyoid bone. The styloid bone starts from the inferior portion of the temporal bone, just medially to the base of mastoid process, and directs inferiorly, medially, and anteriorly, passing anteriorly and laterally to the C1 anterior arch and transverse process. These anatomical structures embriologically originate from Reichert's cartilage of the second brachial arch.

Classic Eagle syndrome is mainly characterized by pain, dysphagia and otalgia, often exacerbated by yawning and swallowing, arising after a tonsillectomy. It is thought that postsurgical scar tissue stretches the sensory nerves ending in the peripharingeal region [28].

The carotid artery variant of Eagle syndrome is due to the impingement between an elongated styloid process and the carotid artery and associated nerves. It is characterized by pain and an increased risk of cerebrovascular ischemic accidents: arterial dissection, obstruction, transient ischemic attack, and stroke.

A third variant of the syndrome has been described, consisting in an IJV compressed by an elongated styloid process in the passage adjacent to the transverse process of C1. The most common involved jugular segment is J3, and in more than 50% of patients the stenosis is bilateral. It is alternatively named "*Eagle jugular syndrome*," "*Styloidogenic-cervical spondylotic internal jugular venous compression*," or "*Styloid-induced internal jugular vein stenosis*" [29].

This latter form of Eagle syndrome has specific features related to an impaired CVS outflow.

Clinical presentation is frequently nonspecific. Most frequent symptoms are

- **Headache** (46.3%): not typically present in the classic and carotid variant of Eagle syndrome;
- **Tinnitus** (43.6%);
- **Insomnia** (39.6%);
- **Visual disturbances** (28.9%);
- **Hearing impairment** (24.2%).

More peculiar, an **increased ICP** is observed in more than one-third of patients (36.2%).

It is more common in young adults (mean age of onset 38.6 years) with no prevalence between sex.

In literature, only 1/3 of patients with diagnosed Eagle jugular syndrome have an effectively elongated styloid process. This suggests that even with a normal length, an

abnormally narrow space between the styloid process and C1 transverse process may lead to IJV compression [30].

Diagnosis is classically radiological, with direct evidence of impaired IJV flow (MRI venography or angiographic venography) or indirect proof of a narrowed C1-styloid space (CT scan or MRI). Few criteria have been proposed, and not diffusely shared between studies, to define a significant IJV stenosis in a setting of suspected Eagle jugular syndrome. According to Jayaraman [31], a jugular stenosis is defined as a caliber reduction >80% on axial cuts compared with the normal vein proximal to the stenosis. Ding and Bai [32] proposed other similar criteria.

More frequently, a conservative treatment is preferred with anticoagulant usage, but in most cases medical therapy has shown no effectiveness on symptoms control.

Invasive procedures are surgical (styloidectomy, C1 anterior arch removal), endovascular (ballooning or stenting), or combination of both. Styloidectomy is the most frequently performed surgical procedure, and major risks are vascular or facial nerve injuries.

On the other side, endovascular treatments are associated with stent migration or fracture, pseudoaneurysm formation, thrombosis, and cranial nerve injuries.

After an invasive approach, more than 70% of patients report an improvement in tinnitus, papilledema, and visual disturbances. Headache, the most frequent symptom, and dizziness usually do not respond to the treatment.

One of the major issues still open regarding the Eagle jugular syndrome is the lack of standardized data, especially on IJV pressure, flow velocity, and collateral pathways. Thus, a complete understanding of pathogenesis is missing.

4.3 Multiple sclerosis

Multiple sclerosis is a complex autoimmune demyelinating disease characterized by a chronic inflammatory response against the CNS. Many aspects of this disease are still unknown, but evidences have increased, through the last decades, pointing toward a fundamental involvement of CVS in the early development of it.

A cardinal observation is that each MS lesion is crossed and split by a central vein, that is to say that demyelination and inflammatory infiltration develop around a vein [33].

From a wider point of view, inflammatory processes in MS seem to be concentrated around venular vessels, more than capillary or arterial [34].

From these data, and others, an association has been proposed between MS and chronic cerebrospinal venous insufficiency (CCSVI), a condition of long-lasting impaired venous drainage from CVS caused by obstruction in extracranial veins. Recently, CCSVI has been associated also with other degenerative processes such as Alzheimer's disease, Parkinson's disease, and Meniere's disease.

A defective valve, hypoplasia, and/or compression of the IJV or the azygos vein, as defined earlier, increase TMP and reduce the ability of glymphatic system to drain toxic catabolites from the interstitium. These peptides then accumulate at the perivenular level and may act as first inflammatory chemotactic activators and further increase oncotic pressure into the perivascular space, worsening the ISF resorption capacity. Generally, perivenular spaces are recognized as an important site of leukocyte trafficking and the potential milestones to modulate immune response.

Measuring CSF dynamic with MRI reveals interesting links between venous function and MS. In clinically isolated syndrome (CIS), conversion to clinically definite MS in the following year has been related to CSF net flow decreasing [35].

In relapsing-remitting MS, a significant reduction in CSF flow at the level of the Sylvius aqueduct was observed compared to control groups [36]. In the early and progressive form of MS, an increase in ventricular dimension has been observed during the first year. This may be related to the impaired function of glymphatic system, and there are evidences that in these patients, a therapeutic flow restoration through endovascular recanalization of IJV is linked to a significant reduction in ventricles and subarachnoid spaces dimension [37].

Moreover, CCSVI is an ultimate cause of decreased cerebral perfusion because of the propagation of retrograde hypertension. There is a linear correlation between flow into the IJV and global brain perfusion [38]. Moreover, in MS, hypoperfusion is a pathological key point that precedes plaque formation and could be a causative agent, provoking damages to the oxygen-dependent oligodendrocytes. Myelin loss and debris occur when the metabolism of these cells is altered, and this is an important inflammatory signal that attracts leukocytes. Thus, inflammation seems to be a consequence, more than a cause [39]. Subsequent BBB disruption causes microbleedings, and iron deposition, coming from hemoglobin degradation, further increases inflammatory response and microbleedings, especially around venular vessels. Consistently, cerebral tissue iron loading correlates with MS-related disability at the Expanded Disability Status Scale (EDSS) [40].

4.4 Perimesencephalic subarachnoidal hemorrhage

A subarachnoidal hemorrhage (SAH) not caused by vascular malformation (such as aneurysm or arteriovenous malformation (AVM) rupture) is a recognized clinical entity usually referred as *sine materia* (without motivations) or non-aneurismatic SAH (na-SAH).

It typically presents with a pattern limited to the perimesencephalic cisterns (typical pattern), sometimes extended to the nearer basal cisterns (atypical pattern). In the majority of cases, the clinical course is benign, with a very low rate of recurrence. At the neuroimaging, no causes of bleeding are detected, neither immediately or later. Pathogenesis of na-SAH is not established, but the most shared hypothesis regards anatomic variations of CVS, particularly of the Basal Vein of Rosenthal (BVR) draining into venous systems different from the Galenic one. CVS hypertension has also been occasionally reported to influence the overall risk of na-SAH in various conditions, such as cavernous sinus thrombosis, transverse sinus thrombosis, or a bilateral jugular venous obstruction.

In a retrospective case-control study, a significant association has been made between na-SAH and the presence of an IJV stenosis (>80% of caliber reduction) at the passage through the styloid process and the arch of C1 [41]. Also, older age and diabetes were statistically linked to an increased risk of na-SAH.

This is coherent with what has been reported before: an impaired CVS outflow due to a stenosis leads to increased venular pressure, thus predisposing wall rupture and bleeding when an adjunctive pressure is applied (e.g. physical exertion). The presence of anatomic variations may be a further element that increases the risk of na-SAH, but, in the end, the way in which venous configuration of the perimesencephalic area might predispose to bleeding remains undetermined.

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