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The Pathology of the Internal Jugular Vein in Multiple Sclerosis

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Abstract

In the last years it has been described a condition named Chronic Cerebrospinal Venous Insufficiency (CCSVI), frequently but not exclusively associated to Multiple Sclerosis (MS), which generated a strong scientific controversy about the epidemiological prevalence and the possible role in the complex, multi-factorial MS ethio-pathogenesis.

However, CCSVI description also stimulated a considerable research activity on the extracranial veins. Among the fields of interest, the pathology of the Internal Jugular Veins (IJVs) was deeply investigated by some groups, so improving our knowledge in an underestimated field of MS research. Currently, the available papers clearly show the presence of abnormalities in the IJV wall of MS patient's respect to control tissue. In the tunica intima a significant derangement and loss of the endothelial cells have been described. Interestingly scanning electronic microscopy showed absence of endothelium in the defective jugular valves. In the adventitia it has been described an inverted ratio between type I and type III collagen, with prevalence of the latter. Finally, in the adventitia layer it has been found the presence of calcifications arranged around the vena venarum. Assessment of immune cells in the three IJV layers did not demonstrate increased infiltration. Current studies do not clarify the origin of the pathology of the IJV in patients with MS. Congenital, infectious, or even post thrombotic ethiology have been advocated. Finally, the review summarizes studies which link the CCSVI pathophysiology to the complex MS pathogenesis, and particularly to the impact of restricted brain outflow on the cerebral spinal fluid dynamics and cerebral perfusion.

Keywords: Multiple sclerosis; Chronic cerebrospinal venous insufficiency; CCSVI; Internal jugular veins; Endothelium; Venous valves; Venous malformations

Introduction

In the last years it has been described in patients affected by Multiple Sclerosis (MS) a venous disorder characterized by intraluminal obstacles at the level of the Internal Jugular Vein (IJV), or sometimes, by segmentary hypoplasia and compression [1-6]. Collectively, this condition is named chronic cerebrospinal venous insufficiency (CCSVI); these IJV abnormalities determine a restricted venous outflow from the brain, and, when also involved the azygous vein, from the spine [7-9].

The reported prevalence of CCSVI in MS and in healthy controls is highly heterogeneous in literature, as demonstrated by several meta-analyses [10-12]. This generated a considerable scientific controversy, mainly linked with the initially proposed Doppler ultrasound protocol apparently affected by low reproducibility [8,13].

To overcome problems in diagnosis and imaging of CCSVI related to the Doppler ultrasound in a recent position paper, the International Society for Neurovascular, Diseases recommends a multi-modality approach [7].

Finally, to complicate the scientific picture, further studies reveal that CCSVI, initially found in MS patients, is also possibly associated to other neurodegenerative diseases and even present in healthy controls [14-16]. However, independently from the problem of imaging CCSVI, which prevents to reliably collect solid epidemiologic data, little is known about the pathology characterizing the jugular venous wall in CCSVI condition. Aim of this paper is to review the histopathology of the IJV described in MS respect to healthy controls, as well as to show why such pathological aspects can be challenging to be diagnosed by the means of current imaging techniques.

The Venous Wall

The structure, function and pathology of the venous system have received comparatively little attention when compared to similar studies on the arterial system. This neglect is the result of a common tendency in medical thought: the presence of disease often dedicates the need for fundamental studies of structure and function. Veins attract little attention except when they are involved in new discovered pathology as CCSVI, thrombosis or in abnormal dilatation such as varicosities in various parts of the venous tree.

All blood vessels have an inner layer, the intima, lined by endothelium with subjacent connective tissue; a middle layer, the media, composed of smooth muscle, elastic tissue and collagen embedded in ground substance; and an outer layer, the adventitia, composed of elastic and fibrous tissue.

The endothelium is a monolayer of elongated epithelium – like cells that form the inner lining of the heart, arteries, capillaries, veins and lymphatics, the individual cells being oriented with the long axis in the line of blood flow. Adjacent cells are connected by tight and gap junctions, the number and proportion of each varying in different parts of the vascular system and in different segments of vessel. An important function of the endothelium is the prevention of thrombosis, an almost invariable consequence of significant breach in continuity of the otherwise smooth lining. The subjacent intimal tissues are highly thrombogenic, quickly initiating platelet adhesion and agglutination followed by fibrin deposition.

The ability of blood vessel to accommodate or influence changes in blood flow and intraluminal pressure by contraction or relaxation rests largely with smooth muscle component of their wall, moderated by

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connective tissue elements and a complex of vasoactive substances and the autonomic nervous system [17]. At one time the smooth muscle was thought to be restricted to the media of vessels but with the advent of electron microscopy and other technological advances such as immunohistochemistry it was established that so called "transitional" or "myointimal" cells, a prominent component of the intima in normal adult blood vessels and also of arteriosclerotic lesions, are smooth muscle cells. Smooth muscle, in contrast to skeletal or cardiac muscle, will replicate and proliferate under appropriate stimuli as seen for example in the repair processes, in response to inflammation, in altered hemodynamic conditions such as hypertension and in atherosclerotic lesions.

Collagen and elastic tissue, the main fibrous proteins, are embedded in a complex ground substance of proteoglycans (acid mucopolysaccarides) and glycoproteins such as fibronectin, already referred to, and laminin the basement membrane glycoprotein. Of the eleven types of collagen described, types I and III of so called interstitial collagens are the major fibrous proteins of the walls of veins with prevalence of type I; they are produced mainly by the fibroblasts of the adventitia but also by smooth muscle cells laminin of the media. These collagens provide the tensile strength of the vessel wall, putting a constraint on its dispensability.

Large veins possess a medial layer composed of bundles of smooth muscle cells embedded in connective tissues. The content of connective tissue exceeds that of the smooth cells. In some of the large veins, like the caval veins, the adventitia is thick and also contains an abundance of smooth muscle cells, usually with a longitudinal orientation. By contrast, the intima is thin in these large veins. The muscular nature of the media is more evident in medium – sized veins but collagen and elastin fibres are prominent between the smooth muscle cells. The adventitia is composed mainly of collagen, again usually oriented in longitudinal fashion, and it appears to be the thickest layer of the wall. The intima is relatively inconspicuous.

The efficient functioning of the venous system depends upon the competence of valves. This thin endothelium – lined structures are so constructed as to support the venous return to the heart against action of gravity. Venous valves occur in many veins, both small and large, that conduct blood flow against the gravity. They prevent the backflow of blood from the heart. There are papers describing the anatomy of valve system of different anatomical district's veins, correlating it with functions and neurological pathologies [18,30]. The valves are slender, semilunar, pocket-like flaps formed by local folding of the intima. Each valve is usually composed of two leaflets positioned opposite each other, with their free edges directed toward the heart. When blood passes throughout the lumen between the leaflets, they flatten out against the wall of the vein. When blood begins to regurgitate the pocket fill up, causing contact of the two leaflets and resulting in closing up of the lumen of the vein. Venous valves are not found in cerebral veins, the superior vena cava, pulmonary veins, umbilical veins, or veins of viscera and bone marrow.

Vein Wall Compliance and Venous Function.

The histology described above is closely linked with the mechanical wall properties of the veins, and particularly with both elasticity and compliance. Compliance (c) is a characteristic of every hollow system, but in veins perfectly fits with the venous function of drainage. Volumetric increase (dV) of the content is correlated with pressure increase (DP) inside the vein (the equation is c= dV/dP); [19-24]. The components of the media layer of veins, described above, permit to the venous system to achieve high compliance respect to artery. (Figure 1) with in the brain 75% of blood circulates in the venous system, because of greater compliance of veins respect the arteries.

If a venous system has high compliance, it can receive a significant volume of blood with a small increase in pressure; the correspondent curve will not be very steep.

Conversely, if the system has low compliance, even a small increase in blood volume within the system causes a significant increase in pressure, and the curve will be steeper (Figure 1).

Jugular vein compliance and postural changes

The IJV needs of high compliance because physiological postural changes determine big variations of hydrostatic pressure especially in the veins of the neck. In up-right posture the hydrostatic pressure is negative, around -30 mmHg; to the contrary, in supine posture it accounts +5-7 mmHg [25]. Passing progressively from supine to upright the hydrostatic pressure becomes negative because the IJV is placed above the heart. This means that the pressure external to the vein (atmospheric pressure) becomes prevalent, and squeeze the IJV which becomes smaller. In (Figure 2) the progressive reduction of the cross

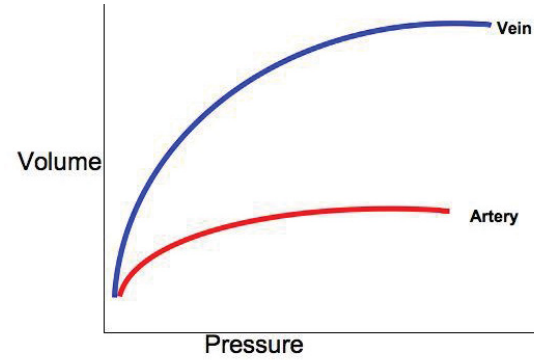

Figure 1: The wall compliance of veins permits, differently from arteries, to increase blood volume with little increase in pressure. The steeper curve of the artery indicates lower compliance.

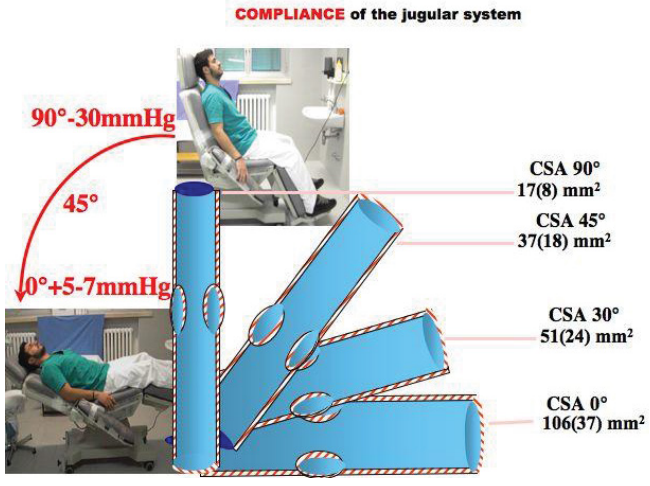

Figure 2: CSA variation changing the hydrostatic pressure with posture in the IJV. CSA is largest in supine, characterized by a positive value of hydrostatic pressure. Passing progressively in up-right the pressure becomes negative, and the external component of the transmural pressure, represented by the atmospheric pressure, becomes prevalent and press the IJV wall. The prevalence of the external pressure over the internal one results in a significantly reduced CSA. Data are derived from reference 26.

sectional area (CSA) of the IJV in normal controls is given, showing the dramatic reduction passing from supine to upright [26]. The variation in CSA expresses the volume variation respect to the variation of the hydrostatic pressure. The big difference of CSA in the two postural conditions expresses the excellent compliance of normal IJV.

Gross anatomy of the IJV in multiple sclerosis and controls

After the description of CCSVI, independently from the difficulty of the clinicians in imaging it in a reproducible way, attention was given to the pathology of the IJV. Normal gross anatomy, describing the natural enlargement of the bulb region of the IJV, it has been recently revised. The Authors show that, normally, the largest CSA of the IJV is greater than 50% respect to the smaller CSA of the vein [27]. The clinical implication is that, evaluating the IJV by contrast venography, the rate of stenosis cannot be calculated by considering the largest and smaller CSA on the entire length of the vein, but rather comparing two adjacent segments [28]. There were reports of post mortem dissection looking for visible stenosis of the IJV in patients with MS. Baiocchini et al. [29] performed complete post-mortem examination of two patients with MS, died for different causes. Postmortem examination demonstrated in both patients a marked stenosis of left internal jugular vein at the apex of the angle formed by the two heads of the sternocleidomastoid muscle, where the IJV overlie the carotid artery, with ectasia and congestion of the intracranial veins.

In a small study Diacunu et al, by the means of an original post mortem technique for examining the extra cranial and extra-vertebral veins, found out valvular and other intraluminal abnormalities with potential hemodynamic consequences in 72% of MS patients vs. 17% of controls [30,31]. IJV septation potentially causing significant intraluminal obstacles to the flow included: circumferential membranous structures (1 MS; 1 control), longitudinally-oriented membranous structures (3 MS), single obstructive septum replacing IJV valve (2 MS), and enlarged and malposition valve leaflets (1 MS). Significant stenosis was seen in 2 MS and 1 control. Additionally, several minor anatomic variations were observed similarly in both MS and controls. These included valves with 3 leaflets, the presence of azygous valves, additional (duplicate) normal-appearing IJV valves, and small accessory valve leaflets.

Gross anatomy of defective valves was also appreciated in course of surgical procedure for severe obstructive pictures in the IJV of MS patients (unpublished data). We observed defective valve cusps characterized by absence of the commissure resulting in a not mobile intraluminal septum, and also valve leaflets with the sinus oriented against the brain outflow (Figure 3). In both cases such structure changes determined significant impairment of the cerebral drainage.

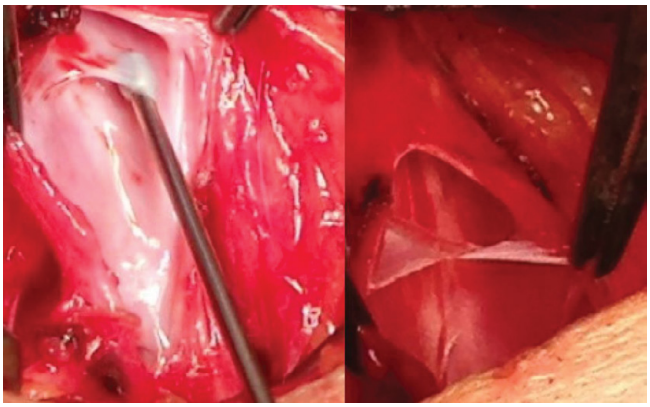

Figure 3: Defective valves of the IJV observed in MS patients. Left: bicuspid IJV valve with up side down cusps, oriented to prevent the cerebral flow. When the valve is open the flow is stopped and cannot reach the chest (upper part of the picture). Right: absence of the commissural separation between valve leaflets resulting in a septum causing primary venous obstruction.

The Histopathology of the IJV in MS patients

The aim of these researches was to investigate the molecular, cellular, and chemical changes occurring in the jugular tissue of CCSVI patients, in order to improve knowledge of the underlying biochemical mechanisms involved in such novel vascular disease, with potential implications in the process of neurodegeneration. The available papers investigate all the three layers of the vein wall, and also the valve leaflets. The techniques used are certainly advanced respect to routinary histological examination.

Abnormalities in the adventitia layer

Among additional approaches to conventional techniques, a group experimented with the potential of synchrotron radiation based X-ray Fluorescence (XRF) microscopy at different incident energies to reveal characteristic chemical features of pathological tissues. X-ray fluorescence analysis is a multi-elemental, highly sensitive technique based on the detection of X-rays emitted from samples' atoms excited with X-ray photons. This technique can provide semi-quantitative or quantitative information since the fluorescence intensity is related to the concentration of the element within the sample. Over the past decade, the investigation of biological samples with XRF has been boosted by the development of high-flux and highly focused X-ray beam at different synchrotron facilities [32-34].

Conventional histology showed in specimen of MS patients affected by CCSVI abnormal deposition in the vena venarum of the adventitia (Figure 3). However, the nature of the deposition was unclear, and for this reason a sequential X-ray Fluorescence (XRF) analyses at three different synchrotrons at complementary energies on jugular tissue samples from MS patients and control subjects were performed [35].

This investigation permitted to evaluate the elemental composition of the anomalous micro-formations. The set-up of the XFM beam line allowed rapid elemental analyses of large tissue areas identifying an increased calcium (Ca) presence in the pathological samples, mainly at the level of microvessels of the tunica adventitia (Figure 4). A deeper elemental investigation with higher resolution set-ups at the ESRF and Elettra synchrotrons at lower energies showed that this high Ca level corresponded to the presence of micro-calcifications, containing P and Mg as well. The reason of anomalous micro-deposition in the jugular tissue of MS patients is not currently known [35].

Altered hemodynamics described in CCSVI acts either on the endothelial cells or on the deeper layers of the vein wall, increasing the mechanical stress on the adventitial intramural vessels [3,7,8,14]. The mechanical overload may potentially lead to the differences demonstrated in calcium contents with respect to the control tissue. From this point of view calcium deposits could be interpreted as the result of chronic stress of the vein wall capillary with mechanical injury and damage [35].

Types I and III collagens are the major matrix components of the mature vessels. Collagen fibers surrounding fibroblast of the adventitial layer are the primary source of the tensile strength of the vessel wall [36-39].

Coen et al found an abnormal content of type III collagen in the contest of the adventitia of the diseased veins, either treated and no

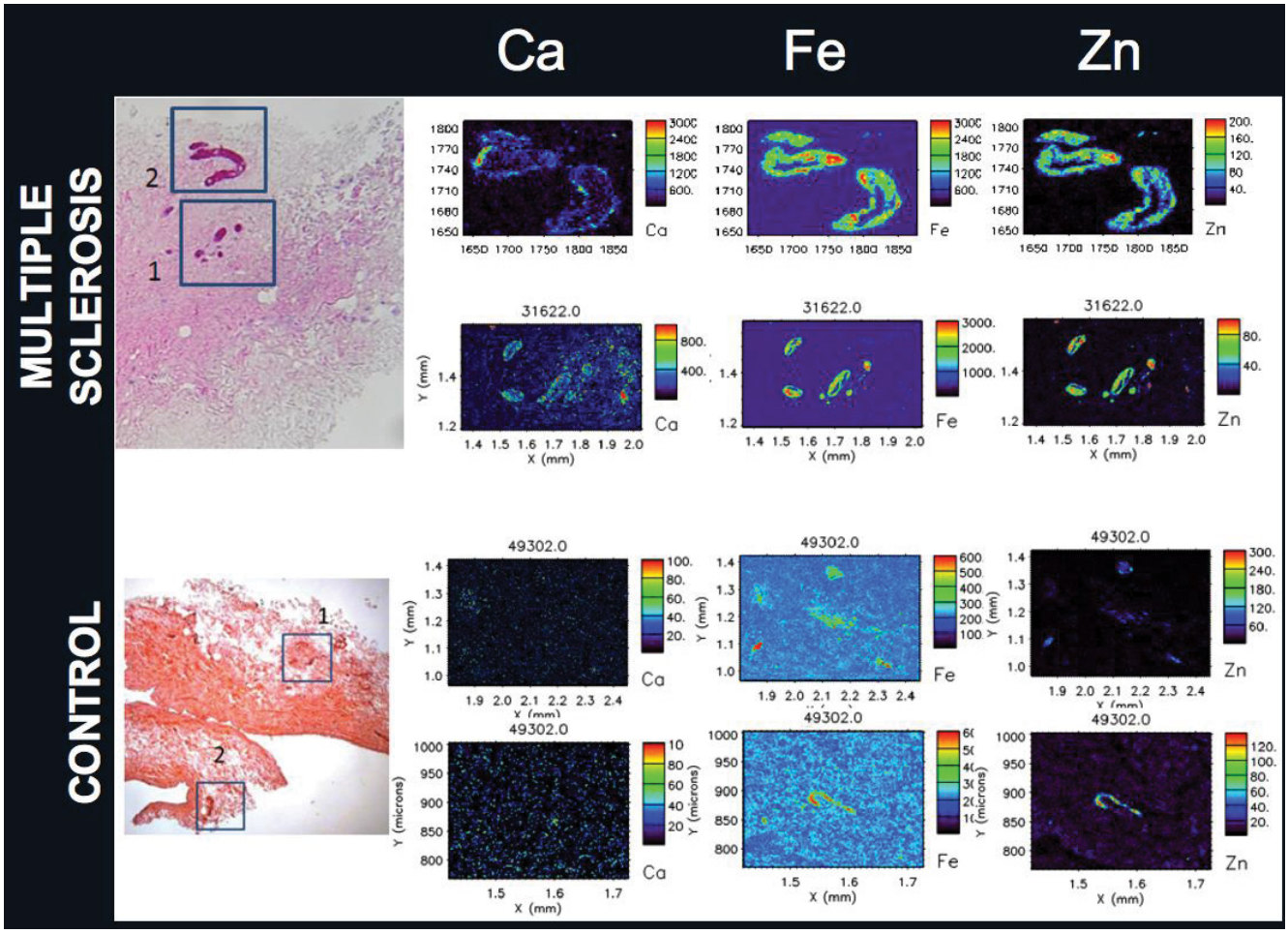

Figure: 4 Light microscopy image of a stained slice of an IJV in a MS patients (top panel) and in a control (bottom panel): boxes 1 and 2 represent respectively the adventitial sub-areas subsequently resolved under XRF analyses. Columns refer respectively to calcium (Ca), iron (Fe), and zincum (Zn) XRF assessment. The concentrations are on the scale bars are given in ppm, and the higher concentration of elemental composition in the multiple sclerosis panel are well evident as compared to control tissue.

treated, respect to the control veins [40]. This finally leads to an altered ratio between type I and type III collagen fibers in the venous adventitia, a factor of pivotal importance in determining the mechanical wall properties of the human vessel, as described above.

Interestingly, also the presence of collagen disorders is relevant to MS. The prevalence of MS in Ehlers-Dalos disease is 10-11 times higher [41]. In addition, type III, I, and V collagen fibres are up-regulated in MS, with abnormal deposition in the perivascular space of the blood brain barrier.

Abnormalities in the media layer

Truncular venous malformations (TVMs) are the result of the developmental problems of vascular trunk formation during the fetal phase; TVMs are subdivided into obstruction, and dilation (aneurysms) [1]. Both obstructive patterns (CCSVI) and dilation, primary aneurysms, have been described as TVMs at the level of the IJV. The latter were frequently found in young people in Sardinia, an island where, by the way, MS is highly prevalent. Microscopic examination showed a thin wall where, in the media, the elastic fibers were found very irregularly arranged. Antisera to both desmin and Alfa-actin, two powerful muscular markers, demonstrated a reduction of smooth muscle cells (SMCs) which, sometimes were organized in sub endothelial clusters [36]. The media layer was also investigated in TVMs of MS patients, who underwent open procedures for severe obstructive clinical pictures. Differently from jugular aneurysms, Coen et al did not find a reduction of smooth muscle cells, but a media with a thin layer of circumferentially oriented SMCs.

In this investigation antibodies CD3 marker of T lymphocytes were also used. The Authors did not find differences in terms of T cell and macrophage infiltration by comparing diseased and control venous walls. Such a finding seems to exclude that CCSVI lesions could be considered a product of the concomitant MS.

Abnormalities of the intima layer

A relevant cause of primary venous obstruction is the presence of intraluminal obstacles such as septa, webs, membranes, fixed and rudimental valves, or wall stenosis (segmental hypoplasia). TVMs may have different hemodynamic impacts on their relevant drained apparatus/organ. Independently from the area where they occur, the impact is chronic and progressive on the clinical course, depending upon their location, extent/severity, and natural compensation through collaterals [1].

Intraluminal defects are considered one of the main mechanisms

causing a significant delay of jugular flow in course of chronic cerebrospinal venous insufficiency (CCSVI), when investigated by an objective standardized catheter venography method [42]. Recently the ultrastructure of the intimal layer of the IJV of MS patients have been investigated by the means of scanning electronic microscopy (SEM) [43].

Control vein showed a virtually intact endothelial layer, with regular disposition of the cells (Figure 5). This appearance changed completely in the diseased specimen, displaying areas of partially detached endothelial cells and the loss of the integrity of the luminal monolayer as evidenced by craters or cavities (Figure 5).

The picture resembles chronic venous insufficiency of the lower limb where the endothelial cells are found detached and irregularly disposed mirroring flow turbulences characterized by a disorder of velocity and flow direction [44]. In addition, these cells showed an increased level of cytokines expression modulated by the abnormal hemodynamics. The morphology of endothelial cells at SEM in the IJV of MS patients is certainly the most resounding aspect of the jugular pathology by comparing with control tissue. There is no need of sophisticated techniques to appreciate the difference because morphology speaks for itself.

It has been proven that CCSVI share the three main risk factors with MS: smoking, vitamin D deficiency and Epstein–Barr virus, all pointing to endothelial cell as the main cellular target [48,49]. Smoking is certainly the most important risk factor for endothelial cell damage, whereas vitamin D has a protective role. Finally, Epstein–Barr virus passes the blood–brain barrier by invading the endothelial cells, therefore, epidemiologically, linking the imbalance of these three factors to MS through autoimmunity [49]. We cannot exclude that Epstein–Barr virus and also other subclinical virus infections may damage the endothelium and the tight junctions of the IJV. Tight junctions are highly specialized membrane domains. Looking at figure 5 bottom panel, they seem severely damaged. Over the past few years there has been increasing evidence that tight junctions can be attacked and damaged by viruses in order to complete their cycle. Viruses from at least nine different families have been reported to exploit the tight junction proteins [50].

Abnormalities of the jugular valve

Stuck, immobile valve leaflets were observed in clinical practice on MS patients in course of catheter venography, external and intraluminal ultrasound [2,7,32]. The clinical imaging mirrors the cadaveric study of Diaconu. It would be expected that a congenital TVM should be lined by something like a single flattened layer of endothelial cells surrounded

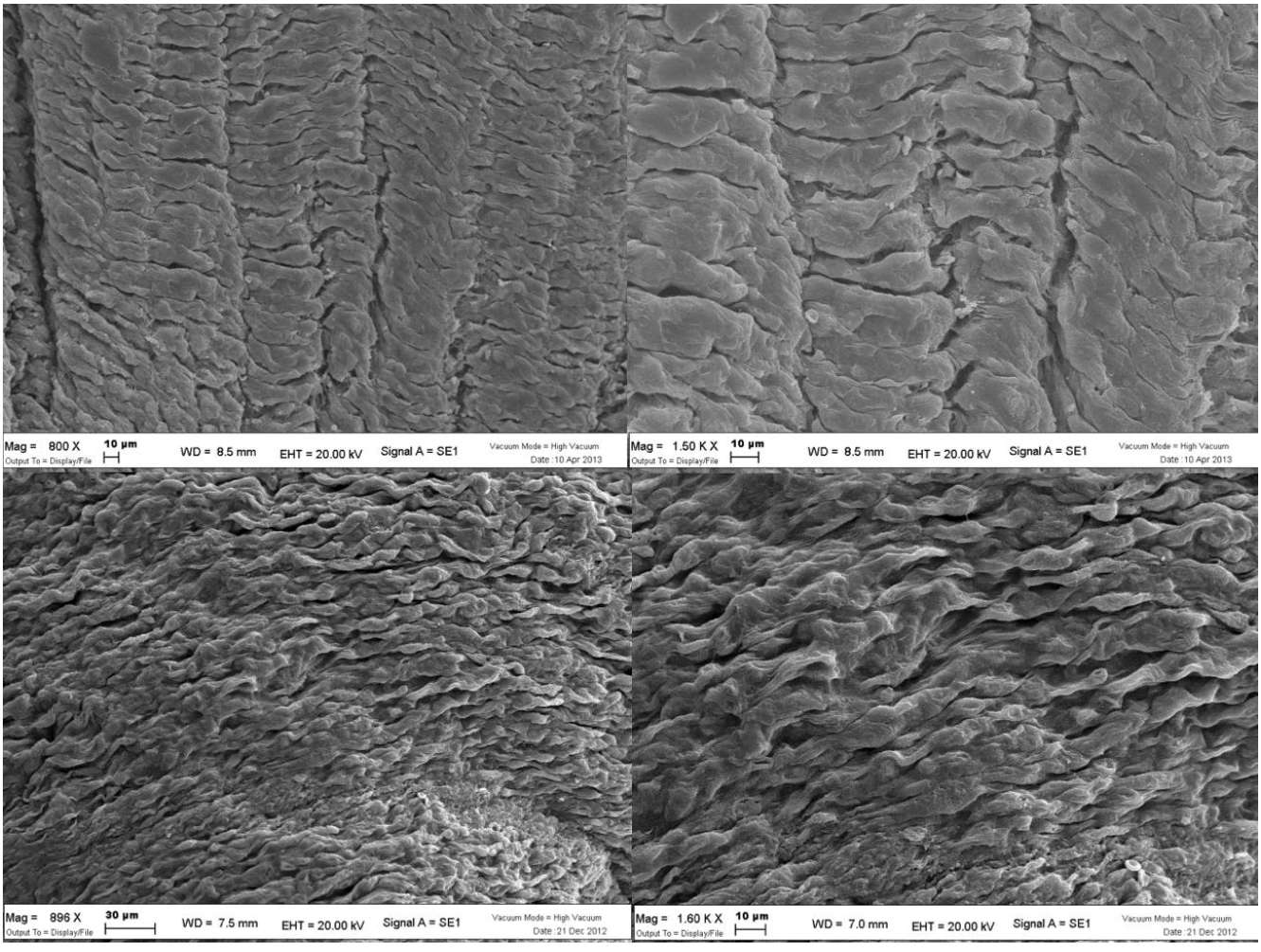

Figure 5: Scanning electronic microscopy. Top panels: regular disposition of the endothelial cells in IJVs of healthy controls, respectively at 800x (right) and 1500x (left). Bottom panels: irregular arrangement of the endothelial cells in the IJV of a MS patient, respectively at 800x (left) and 1500x (right). The cells appear lifted with craters.

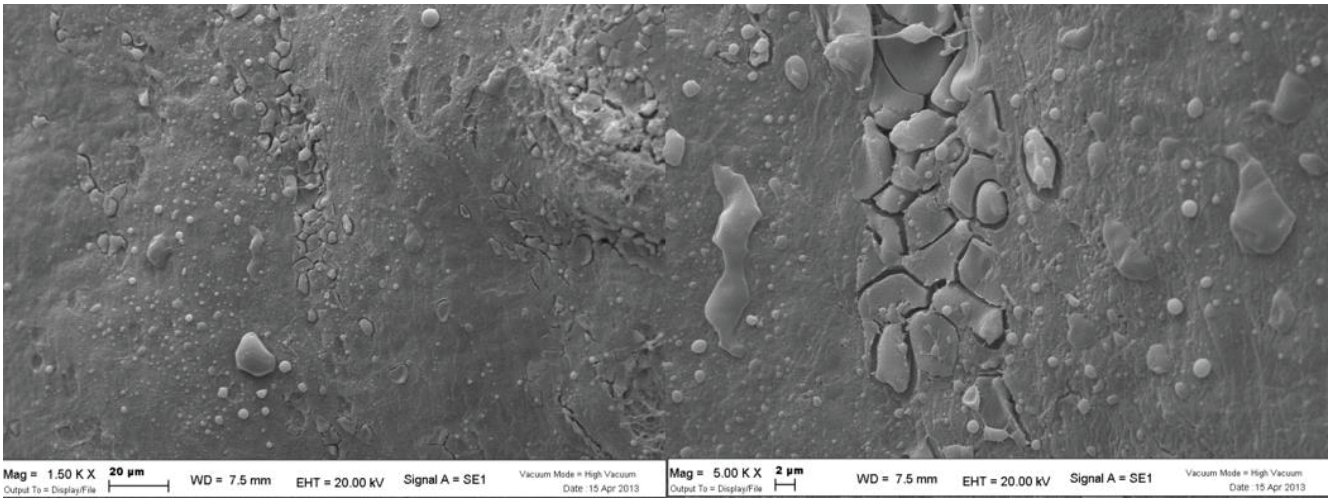

Figure6: Scanning electronic microscopy of the surface of an IJV valve in MS, left at 1500x and right at 5000x respectively. The lunatic landscape in consequence of the absence of endothelial cells is well apparent. It remains a fibrotic lamina, sometimes corrupted and slightly raised.

by sparse, irregularly distributed SMCs. When defective valves were observed at SEM, the more surprising finding was the absence of endothelial cells in the examined specimen. In addition, a reticular and fibrotic lamina replaced the endothelial layer. This finding opens, of course, new questions about the origin of defective valves. The aspects of the valve surface showed in Fig. 6 cannot exclude that intraluminal fibrosis could be a result from a past, resolved inflammatory or thrombotic process that involved the wall of the IJV. From this point of view some authors quite recently hypothesized a post infective origin of CCSVI in course of MS, focused on clamidia pneumofila [46,47].

Cerebral venous drainage consequences of IJV pathology

The above described pathology of the IJV determines a restricted venous outflow from the brain through the major route, with increased flow through the collateral veins. In CCSVI cases it has been measured a significant delay of the extracranial venous flow respect to normal controls, with different methodologies for flow assessment. Strain-gauge plethysmography showed a faster flow in healthy controls when they pass from supine to upright posture, 2.73ml/sec on average, respect to MS patients who discharged the venous blood through the neck at 1.73ml/sec [51]. Same conclusions were drawn by Doepp et al. measuring flow in the upper part of the neck by the means of echocolorDoppler. The Authors demonstrate a much larger change in blood flow in normal subject compared to MS patients when the subject go from supine to upright position [52]. Veroux et al., by the means of catheter venography, measured a cut-off of 4 sec to separate normal from abnormal contrast dye clearance time, following a standardized injection in the IJV. Almost 80% of MS patients showed a delayed clearance time in at least one IJV [53]. This result was mirrored by Mancini et al by the means of contrast enhanced ultrasound, which demonstrate a significant reduction of clearance time in the IJV of MS patients respect to healthy controls, when injected with standardized contrast micro bubbles [54]. Interestingly these Authors also found a significant inverted correlation between the delayed IJV contrast clearance and the level of disability, since slower flow corresponded to higher expanded disability severity score.

All the above studies show a slow flow through the major extracranial outflow pathways with increased drainage time than expected. Such functional parameter is normally used to define a condition of chronic venous insufficiency, regardless the organ or apparatus were the insufficient drainage time is assessed. This is the reason why, measuring slower flow in the major veins draining the central nervous system of MS patients, the condition was defined chronic cerebrospinal venous insufficiency. Finally, it has been shown how in MS patients the brain in-flow is not significantly different respect to controls. To the contrary, brain out-flow is significantly restricted, with increased proportion of the brain in-flow which is drained through the collaterals route [55].

The pathogenic hypothesis linking CCSVI to MS

In the previous paragraph the hemodynamic consequences of IJV pathology have been shown, as well as the reason of the definition CCSVI. One of the more important questions answered by the research in the last years was to understand what is the impact of CCSVI in brain pathophysiology. Evidences repeatedly showed us two major consequences, the first is the reduced absorption of the cerebral spinal fluid (CSF) in the dural veins, and the second is a reduced perfusion.

i) CSF dynamics impairment in MS. It has been shown in CCSVI patients a slow CSF flow by the means of MRI at the level of the aqueductus of Sylvius [56]. The absorption of the CSF from the sub-arachnoideal spaces to the dural veins is a physical mechanism based on a gradient of at least 5mmHg between the 2 compartments. The hypothesis that reduced CSF dynamics might be linked to CCSVI was further corroborated by a case control study. Following venous angioplasty aimed at improving flow through the IJV the CSF flow was significantly better over 6 months follow up in the operated patients respect to patients who were followed up without procedures [57]. Impairment of CSF flow links CCSVI to MS, also because it seems a significant prognostic factor. For instance the probability for a clinically isolated syndrome to evolve into a clinically defined MS is increased in people with reduced CSF flow at MRI. Moreover, the latter condition also determines a higher risk of accumulated T2 lesion [58]. ii) In CCSVI cases associated to MS it has been measured a reduced brain perfusion at MRI [59]. The same was reported by a group of the Wayne State University which demonstrated a correlation between the IJV flow measured by the means of objective 2D MRI and brain perfusion (Figure 7). Interestingly perfusion was less efficient in cases with reduced IJV flow [60]. The above studies for the first time linked brain perfusion to the venous outflow. This is particularly intriguing in MS

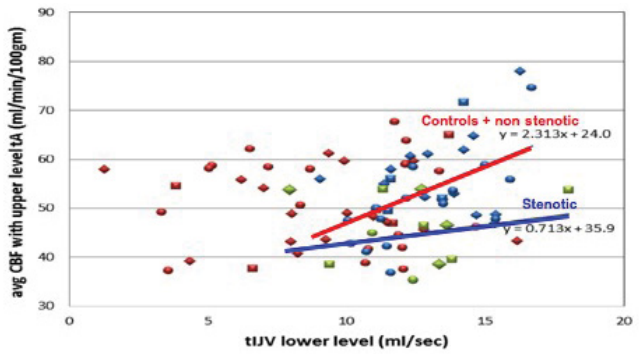

Figure 7: Brain perfusion correlation to IJV flow objectively measured by the means of 2D MRI in healthy controls and MS patients with absence of IJV stenosis (red line) as compared to MS patients with stenotic jugulars. The impaired brain perfusion in the latter group is well apparent. Courtesy to Dr Mark Haacke, Wayne State University, Detroit, USA

because chronic hypoperfusion is a well-known aspect not attributable to autoimmunity [61]. For instance hypoperfusion precedes plaques formation [62]. Oligodendrocyte is particularly vulnerable by reduced perfusion, and speculatively we may hypothesize that demyelination could be related to less efficient mitochondrial activity and myelin synthesis in these specialized cells. This seems to be confirmed by the observation that in early stages axon injury and loss of myelin are documented in the absence of any inflammatory and immune cells infiltration. Only subsequently macrophages migrate to take-up myelin debris, which are powerful chemo-tactic stimuli [63,64]. We believe that the contribution of brain drainage to inflammation, perfusion and CSF flow warrants further research because are all aspects involved in the complex MS pathogenesis, where the contribution of the IJV restricted flow in consequence of the IJV pathology cannot be further neglected.

Conclusion

The major outflow route from the brain in MS patients readily shows significant changes in all the venous layers as well as in the valve. In this particular moment limitations in the clinical imaging of the IJV do not permit to know the real prevalence of CCSVI in MS patients. However, the pathological aspect herein presented represents an intriguing field of research. In perspective, future investigations should be aimed in linking the extracranial and extra vertebral venous pathology to the complex and multi-factorial pathogenic scenario of MS, a neurodegenerative disorder still of unknown origin.

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