Chronic cerebrospinal venous insufficiency in multiple sclerosis: Weighing the findings

Franz Schelling

Fingstr. 32, 6974 Gaissau, Austria
<dr.franz.schelling@gmail.com>

Abstract Chronic cerebrospinal venous insufficiency (CCSVI) proposes hindrances to the venous drainage of the brain and spine. Clinically diagnosed or definite multiple sclerosis (CDMS) is diagnosed by a “dissemination in space and time” of brain and spinal cord lesions in want of a specific characterization. This definition of CDMS and its attribution to auto-immune mediated demyelination (somehow also destructing axons) has never been proven and complicates the assessment of its role in CCSVI and other venous anomalies in the development of conditions categorized as CDMS.

In this review, post mortem and serial MRI observations made in historically specific instances of multiple sclerosis are focused on. They demonstrate the existence of venodynamic lesions that can only be explained by the forceful impacts of fleeting venous flow inversions (FVFIs) which may be of very short duration. To understand the venodynamics of this typical, or “VDMS” it is necessary to determine the source of the venous impacts and how they are directed and limited to the lesion domains. Understanding these venous flow dynamics is critical for evaluating the significance of CCSVI in general; it further seems indispensable for ensuring the success of venoplasties; and it is crucial to the development of alternative rational treatment options in those instances of CDMS in which interventions for CCSVI do not achieve the intended results.

Key words: chronic cerebrospinal venous insufficiency, clinically definite multiple sclerosis
potentielle de cette affection. Pourtant un certain nombre d’observations anatomopathologiques post-mortem et d’imagerie par résonnance magnétique mettent en évidence des anomalies propres à la SEP qui ne pourraient être expliquées que par l’impact de l’inversion brutale du flux sanguin au sein de certaines structures du drainage veineux du cerveau et de la moelle. Une analyse fine de la pathologie, notamment par l’IRM, peut fournir des indications sur le ou les siège(s) de l’inversion du flux veineux, préalable indispensable à toute intervention endovasculaire susceptible de rétablir une hémodynamique veineuse satisfaisante.

Mots clés : insuffisance veineuse cérébrospinale chronique, sclérose en plaques

CCSVI and CDMS: An uneasy relationship

CCSVI

Prototypical CCSVI (chronic cerebrospinal venous insufficiency) is flow reversals in inner jugular, vertebral, or inner cerebral veins and signs of hindrances to normal flow in the inner jugular, vertebral and azygos veins in varying associations [1, 2]. Mainly due to the difficulties in evaluating intracranial venous flow, the original diagnostic criteria for CCSVI have, as a rule, been substantially truncated.

CDMS

Clinically diagnosed or definite multiple sclerosis (CDMS), on the other hand, grounds in a clinical convention. In 1965 a dozen of neurologists agreed to clinically redefine MS as a matter of days and months through which unexplained neurological dysfunctions persist and pause. The reason for this step was to facilitate the selection of comparable populations for MS drug trials [3]. CDMS criteria went on to be continually modified in adding and changing complementary laboratory and imaging criteria [4, 5] for diagnosing MS on the all-embracing principle of “lesion dissemination in time and space” [3-5]. Autocratic neurological authorities asserted that CDMS was attributable to a process of inflammatory demyelination, further specified as immunological autoaggression. This clinical conception and its pathogenic interpretation deny well documented and commonly quoted post mortem observations on multiple sclerosis. As there is no evidence for a distinct CDMS pathology or agent, CDMS is a dubious basis for evaluating the pathogenic significance of CCSVI.

Historic evidence on MS of the brain

Observations of a vein- (not venule !) dependent lesion-spread in exemplary MS specimens, are key-evidence for understanding the significance of CCSVI. A comprehensive review of pertinent literature reveals this [6] (figure 1).

Pioneering post mortem observations

Figure 1(A) is the earliest illustration of the way in which MS invades the cerebral hemispheres [7] [6: Plate IV, figure 1]. The lesion is seen to have spread out from the center into the periphery of the inner cerebral veins’ territory (Charcot 1866, 1867, 1884). First to notice this relationship was Alexander Bruce (Dawson 1916). Later accounts show grotesque deformations and dilations of lesion veins and their perivascular spaces (Dawson 1916, Putnam & Adler Alexandra 1937, Fog 1965, Allen Ingrid 1981). At times, blood or fibrin is seen leaking from veins (Adams 1989) which elsewhere give rise to typically eccentric lesion expansions bursting sometimes forth just to one side of the vein (Scheinker 1947, Fog 1965). The findings can only be explained by crude physical impacts exerted from inside these veins [6].

Cranial MRI evidence

From 1981 onwards, magnetic resonance imaging (MRI) confirmed and expanded on these post mortem findings: In the brain, the outer angle of the lateral cerebral ventricles is obviously the area being primarily affected. This site, the zone of convergence of all the tributary vessels of the brain’s large inner collecting veins, is referred to as “Steiner’s Wetterwinkel” (“Wetterwinkel”, in German, is a corner particularly aimed at by tempests and deluges)
Here lesions are often seen to start as tiny spikes and ripples. But there also arise more extensive lesions likened to knuckles, fingers, bumps or waves – so-called Dawson’s finger formations. Such tend to persist while separate peripheral lesions (Steiner’s splashes) rather disappear, reappear, varying in form and enhancement pattern [8-10]. The only explanation possible for all these different lesion eruptions is fleeting venous flow inversions (FVFIs). They burden their paths’ wide proximal parts first and then spread peripherally simply depending on the momentary balancing of intra- and perivenous pressures. In considering the dynamics of FVFIs, three observations are of special interest:

1. Destruction of tissues tends to be of a higher degree not in larger but smaller lesions [11]. This speaks for a higher prevalence of small volume high speed FVFIs being able to push farther back into the venous periphery. In fact, lesions deep in the substance of the brain were seen to be localized to bends or ramifications of veins, as modeled and described by Fog [6]. Such findings reflect a plain principle of physics: The higher the speed of a FVFI, the more its thrust will become manifest at deviations, bifurcations and narrowings of its course.

2. Lesions do not usually turn up in showers, or rash like, many at a time [10]. Here the strict limitation to the volume of any FVFI in the rigidly enclosed cranio-vertebral space again comes into play. This volume can be used up in a single large lesion expansion burdening some particularly quickly and easily reached rootstock of veins in isolation. Slower, more voluminous, FVFIs appear apt to cause large, well circumscribed lesion expansions showing throughout the same, often remarkably slight tissue changes (so called “shadow plaques”). If they form just a peripheral halo of fibrillary gliosis this is simply a reaction to less intensive mechanical strains [6].

3. Experimental evidence for the role of FVFIs in VDMS is this: While injecting cerebral veins at post mortem Schlesinger realized: Lesion patterns as found in MS can be produced by retrograde overfilling of inner cerebral veins [6]. Lesion veins first expand, and then they dwindle away. A study of the inner cerebral and peripheral lesion-penetrating veins on enhanced MR angiography in obvious instances of VDMS revealed this. The internal draining system of the cerebral hemispheres is involved as a whole. In early and especially in active stages, the inner cerebral veins and...
their main tributaries tend to slightly dilate; periventricular veins, especially those penetrating lesions, show up in larger numbers, dilate and elongate. With older, inactive lesions, all the veins, from largest to smallest, begin to dwindle away, large veins become unsmooth and slightly discontinuous, small peripheral ones appear reduced in number, thinned and shortened; and all this even if lesions could be detected in the spinal cord only, forming lengthy stripes involving its broadest part (details below) [12].

**Cord injury by subarachnoid volume shifts**

Intensified subarachnoid flow readily damages the surface of the medulla [6; review by Mayer]. Bulk flow rather strains the spinal cord along and between its stronger outer fixations. Scars were accordingly seen to extend both across the cord and occasionally all along the line of insertion of the dentate ligaments in severe instances of VDMS [7, 13]. Also in the absence of crude outer impacts, the spinal canal can become the site of intense volume shifts [18, 19]. These will mainly be caused by abrupt compressions of engorged prevertebral collecting veins (cava, azygos, renal and ascending lumbar veins).

Quite remarkably, histologists focusing on the spinal cord spoke of MS as a (primary) scarring process. Those who studied the brain spoke of (primary) demyelination [6]. No wonder: In VDMS of the brain it is the vein walls which bear the brunt of the physical impact from the FVFIs. In VDMS of the spinal cord it is the fibrous structures joining or connecting strict fixation points which are strained first.

**Spinal cord lesions due to ligaments**

Medical history shows it was peculiar scars in the spinal cord discovered together with a scattering of roundish lesions over the pons that established MS as a distinct condition. Discovered in post mortem specimens in the 1830s, the findings became the subject of lithographs by Robert Carswell and Jean Cruveilhier. While Lumsden subsequently realized that pons and brainstem lesions are equally vein-related as those in the cerebral hemispheres, the special nature of spinal VDMS was commonly overlooked.

**Piecemeal lesion specification**

Spinal VDMS was first recognized as something distinctive on account of its somewhat jagged out scars which extend along and into the two sides of the spinal cord. Similar changes were found to occur along especially posterior but also anterior midline of the spinal cord [6, plates iii, iv, v]. Charcot twice depicted the same kind of damages to the spinal cord. Each time, the bilateral spinal cord area affected ended abruptly with the dentate ligament’s uppermost insertion point [6, 7] (figure 1(B)).

A tendency for right and left-sided spinal cord lesions to interconnect or also join posterior lesions in crossing grey matter was highlighted by Charcot (figure 1B) and Falkiewicz [13].

David Oppenheimer finally realized, in 1978: Spinal MS relates to the dentate ligament [14].

**CDMS: Not the Gold Standard for rating CCSVI**

CCSVI in CDMS: Parallel neurological and venous dysfunction?

Speculation rather than insight governs discussions of how CCSVI might further manifestations and progression of CDMS. Nothing is said on the point of how CCSVI may contribute to the so-called “CDMS typical” lesion developments. The issue of how CCSVI relates to brain and spinal cord pathology must not be sidestepped. Dwelling on commonplace phenomena or aspiring simply to show therapeutic success is a shortsighted approach, particularly given the declared lack of neurological professional interest in advancing the cause of CCSVI. No scheme used for diagnosing CDMS can tell us anything about the nature of CCSVI anyhow. And to be frank: Standing for ‘unexplained neurological dysfunctions finding no better explanation than MS’, a diagnosis of CDMS demonstrates only that the neurologist could reach no better verdict.

**CCSVI a hoax?**

What led to the discovery of CCSVI was a sincere attempt to trace the reasons for venous findings in CDMS. Using the ambiguous term of venous insufficiency in naming and interpreting the given observations as a state of stasis has resulted in confusion. Obstructions of main venous pathways of brain and spine by themselves cannot cause...
the lesions of VDMS. If a venous occlusion damages the brain it effects a correspondingly localised congestive encephalopathy, which may be attended by bleedings or intracranial hypertension; in affecting the spinal cord it causes a congestive myelopathy attended rather by a compressive myelopathy due to complicating bleeding. Claiming CCSVI was a hoax was made all too easy: Neither the fluctuation in the symptoms nor the sporadic eruptions of lesions on serial MRIs in CDMS match a static venous anomaly.

**Zamboni’s liberating coup**

There is a further paradox which seems, at first sight, to wholly cut the ground from under the very founding premise of CCSVI: It is the remarkably low trans-stenotic (resting!) pressures measured in affected jugular and azygos veins. This finding nonetheless offers the key to solving the riddle. For a narrowing of the transverse sinus, high up in the venous drainage of the brain, to be (usually rightly) considered to play a part in the emergence of intracranial hypertension, its trans-stenotic pressure gradient has to exceed 10 mm Hg and may even reach 50 mm Hg before being deemed pathogenically relevant.

In CCSVI, trans-stenotic (resting) pressure gradients of a mere 1 or 2 mm Hg were found to attain significance, in many patients with CDMS, as far down as the lower end of a small left internal jugular vein. That pressures having such a limited peripheral effect and resulting in such a negligible degree of stasis can constitute a threat on account of intervening events and circumstances was shown only by drastic and lasting improvements in many a CDMS (or rather VDMS) patient’s neurological and mental state after angioplasty for CCSVI [1, 2, 20].

**From CCSVI to FVFI: Understanding VDMS**

**Meaningful functional findings**

The first two of Zamboni’s five criteria for diagnosing CCSVI do not refer to signs of venous obstruction but to venous reflux in the internal jugular (and/or vertebral) vein and further, most importantly, to reflux in deep cerebral veins [1, 2]. This reflux in intracerebral veins is scarcely studied in patients. Yet it is the very CCSVI finding which shows what damages the brain in VDMS (and most instances of CDMS).

**Venous reflux or FVFI**

Venous reflux is extremely changeable. It ranges from slight and slow regurgitation to hard back jet, can be an accidental or recur as series of ‘battering ram’ impulses. At times reflux is understood as normal venous return or some persistent venous flow reversal. To avoid such misunderstandings a short pushing back of blood in any venous periphery is here defined as a “fleeting venous flow inversion” (FVFI).

**CCSVI paradox**

Understanding the interrelationship of CCSVI, FVFIs and VDMS depends on answering the question: How can trifling degrees of overfilling and negligible increases in the outflow resistance of internal jugular or azygos veins enhance FVFIs to such an extent that they may injure the brain and/or spinal cord? The problem has not been researched. The circumstances in which the emergence, reach, intensity and eventual injuriousness of FVFIs depend shall now be reviewed.

**FVFI basics**

Compression of a vein that, as seen in CCSVI, cannot empty with normal ease in the direction of the heart first drives its blood into low pressure collateral vessels. Depending on these vessels’ width and reserve capacity the shunting of FVFI volumes varies widely. FVFIs having sufficient volume and pressure reach out into the venous periphery. The peripheral spread and effects of FVFIs thus depend on suprastenotic peak pressure and volume and their ultimate speed. All of these are critically modified by the degree of prefilling up to pre stressing of the involved venous periphery. These principles apply:

With a rising degree of suprastenotic engorgement FVFIs first attain larger volumes but then, with increasing pre-stressing of the venous periphery, instead develop higher speeds. A blood column translating a sudden rise in suprastenotic pressure into the venous periphery may exert considerable thrust. Within the firmly enclosed craniovertebral space the exponentially diminishing compliance (potential to yield in form of a compensatory venting) of separate vascular compartments and an as yet unreached venous periphery eventually puts a stop to any FVFI’s advance – the larger the FVFI-burdened venous territory, the sooner this happens. What definitely limits the spread of any FVFI into the brain or spinal canal is therefore, if its volume or momentum is not exhausted before, the balancing of its thrust by its own instantaneous raising of perivascular pressure. Up to this moment FVFIs first overload large proximal veins; then, the higher their speed the more specifically, they affect bends, ramifications or narrowings of their path.
CCSVI no must for VDMS, VDMS no must in CCSVI!

Critical permanent co-factors

Underdevelopment or lack of ordinary channels of collateral venous drainage plays a decisive role in limiting the spread of FVFIs in a particular part of the brain. Weak or absent venous interconnections at the so-called confluence of sinuses are of particular interest: This not only because of limitations to the cross-over flow from one to the other lateral sinus respectively internal jugular vein via confluence of sinuses. What is an even greater risk are predispositions to a preferential burdening of the small and rather strictly demarcated territory of the internal cerebral veins. This is not so much because its collecting veins lack in broader interconnections and because FVFIs here hardly encounter sharp angles or turns in their paths, so that the veins branching out around lateral and third ventricle can be easily assailed. What makes matters far worse is the disposition to a copious compensatory emptying of venous blood from the wide meshwork of large cortical veins: The build up of perivenous pressures capable to stop the advance of an FVFI may become fatally delayed. Far off vein stenoses in venous drainages of the spine may raise the risk in enlarging the blood volume which such FVFIs can displace out of the craniovertebral space; as any FVFI’s vein of origin is intermittently exposed to pressures of up to hundreds of mm Hg, 1 or 2 mm Hg of increased outflow resistance from well filled, compensatorily emptying, spinal epidural veins in a stenosed azygos or left renal vein are no longer relevant.

Functional versus preformed stenoses

The preformed, mainly intramural vein stenoses of CCSVI cause permanent, usually slight, increases in supratessonic vein volume and pressure. In restraining the speeding up of the normally directed flow during vein compressions the venous stenoses’ efficacy is multiplied. This short term effect attains special significance with ‘functional’ stenoses: Dependent on movements and positions, all sort of organs and tissues, above all muscles, exert pressure on extra-cranial and prevertebral veins for varying periods of time. Resultant functional stenoses can work as a factor by themselves or interact with CCSVI stenoses, variously modifying their efficacy. They may even contribute more to VDMS than the preformed stenoses of CCSVI. Corresponding sporadic narrowings play a role mainly along the internal jugular and deep cervical vein, and to some degree along the prevertebral veins. Along the internal jugular vein functional obstructions can be brought about by the digastric muscle in its upper, the omohyoid muscle in its middle, and the anterior scalene muscle in its lower length. The closer any obstruction is to the heart, the more blood the sternomastoid muscle can drive back in direction of the brain (figure 2). Deep cervical veins (figure 3) are liable to be simultaneously obstructed as compressed between the underlying semispinalis cervicis, as well as the straight and oblique capitis muscles on the one hand and the overlying semispinalis capitis, trapezius, and sternomastoid muscles on the other. More or less massive FVFIs can thereby surge back via the condylar and mastoid emissary veins into the lateral sinus during extension, lateral flexion or rotation of the head.

Arterial vein stenoses

Dependent again on positions and movements, venous pathways of brain and spine can also be obstructed and compressed by arteries. Flattening of the left brachiocephalic vein between sternum and aortic arch or branches is frequent. Internal jugular veins can be affected by distorted carotid arteries. The squeezing of left renal veins between aorta and superior mesenteric artery (Nutcracker syndrome) easily leads to an overburdening of sacrolumbar veins – to which pressure of right common iliac artery pressure upon left common iliac vein (May-Thurner syndrome) can also contribute. Pulsation of a compressing artery against a compressed vein itself will thereby hardly affect the venous periphery, except if its vessels are considerably prestressed.

Pulsatile FVFIs

Cerebral and spinal venous reflux is known best from arteriovenous fistulae. Here suprastenotic venous excess pressure is substituted by diastolic arterial pressure, resulting in a hard prestressing of the venous periphery. Arterial pulsation therefore often leads to compressive and constrictive myelopathy. Although arterial pulse is less abrupt than FVFIs, the forms of tensile stress which damage the cord in VDMS also deserve attention in cervical myelopathy attending hypertensive encephalopathy. In spinal arteriovenous fistulae they are, owing to small pulse volumes, scarcely of relevance.

Figure 2. Zones of intermittent muscular obstruction of the internal jugular vein: Overcrossing by digastric (a) and omo-hyoid muscle (b); undercrossing by upper anterior scalene muscle (c) under overlying sternomastoid muscle (d).
Figure 3. Connections of deep cervical vein (a) to lateral sinus (b). A) Condylar (c) and mastoid emissary veins (d), seen from behind. B) Conductivity of the osseous bottlenecks in the venous drainage of the posterior cranial fossa. Origin of right (JD) and left internal jugular vein in sigmoid sinus (JS) compared to right (CD) and left condylar emissary vein (CS) and right (MD) and left mastoid emissary vein (MS).
Cord damaged by collateral venous flow

In an interesting observation, stenosis of both internal jugular veins close to their upper bulb first raised cerebrospinal fluid pressure, causing hypertensive hydrocephalus. Dilation of epidural veins bypassing the stenoses subsequently damaged the upper cervical cord [21]. Speeding up of the collateral epidural venous flow by arterial brain pulsation necessarily worsened the situation.

Vital diagnostic challenges

A systemic approach is exigent

In any FVFI all the involved venous pathways must be seen as a functional whole. In the craniovertebral space, moreover, systems of directly FVFI-burdened, and systems of separate compensatorily emptying venous drainages (whose making room may be far off) have to be discriminated: In the brain and spinal canal, the expansion of FVFI-exposed veins can only be as fast, massive and extensive as the compensatory venous outflow from separate veins of the common space can be speeded up and its speeding up kept up. The risk of FVFI into particular veins of the brain is the higher the less their volume can become dissipated via extra-, trans-, and intracranial collateral channels. Thereby the widely variable caliber of the immediately, or compensatorily, burdened dural sinuses and emissary veins (and their bony bottlenecks in particular), assume critical importance. In two cases out of three, the straight sinus relates the left rather than the right internal jugular vein. How exclusive the connection between straight sinus and internal jugular vein thereby attains an eminently critical role.

FVFI targets vary from person to person

A tracer or contrast injected in an arm vein can all too quickly turn up in particular cerebral veins: in the territory of the vein of Labbé [22] or in posterior veins of the brain [23]. As in the damage done to Wetterwinkel veins and adjacent tissues in VDMS (CDMS), the circumstances and forces responsible for the abnormal venous dynamics have yet to be identified. In 1982 and 1989 early attempts to address these questions, starting with post mortems in CDMS in seeking to find instances of VDMS (figure 4), met with resistance on the grounds that CDMS (and thereby also VDMS) were assumed to be autoimmune in origin.

Figure 4. Structures of relevance for the course of FVFIs in venous drainages of the brain: Valves of internal jugular veins (a), confluence of sinuses (b). A) Injection preparation of two confluence variants. B) Methods of an early attempt at their evaluation.
A few suggestions on how to approach these problems remain to be addressed.

**Sourcing the FVFIs causing VDMS of the brain**

In the post mortem and MRI findings of an exclusive overburdening of Wetterwinkel veins made in CDMS as in the aforementioned observations of a tracer or contrast being driven back into Labbé’s or posterior veins of the brain we know where the FVFIs’ target area and have to retrace its route to its origin.

Focusing on a person’s Wetterwinkel lesions, we have to first answer the question: Is the straight sinus, through which FVFIs must pass, better accessed via the left lateral (or occipito-marginal) sinus or the right one – or is there no difference?

If there is no difference, specific overburdening of Wetterwinkel veins can only be accounted for by high-speed FVFIs reaching the Dawson’s fingers and Steiner’s splashes domains somewhat earlier than cortical and/or spinal epidural veins.

If it is clearly one of the lateral (or occipito-marginal) sinuses by which the Wetterwinkel veins are more easily reached, pre-formed or functional stenoses have to be looked for along its main connection(s) down to the heart. Valvular incompetence of the internal jugular vein also allows FVFIs to surge back from the chest.

Registering the local FVFIs’ suprastenotic peak pressures would allow their risk to be assessed in some way. To properly define their injurious potential, however, simultaneous monitoring of upper intra-ventricular pressure would be required.

**Special problem spinal FVFIs**

The dynamics of volume shifts in the spinal dural sac and their ways of straining the cord are problems of their own – see earlier reference to the involvement of the dentate ligament. As for the location of the effects of their injurious overdoing, subarachnoid straits and strictness of cord moorings play a decisive role. As a result, location of cord lesions and (epidural) FVFI target zones do not usually correspond. Locating harmful FVFIs is more difficult here. As for the course of FVFIs resulting in impetuous volume displacements in the spinal canal and its subarachnoid space it may be useful to remember these facts:

Spontaneous rises in pressures inside the trunk burden its veins quite evenly but the diaphragm causes intermittent increases of abdominal over thoracic pressure. Such excess pressures cause concerted FVFIs into the thoracic and sacro-lumbar spinal canal as a whole or into the sacro-lumbar spinal canal alone. Mooring lesions affecting the cervical cord only thus point to FVFIs burdening veins at subcervical levels. Such located in the lowermost cord indicate preferential involvement of intra-abdominal and sacro-lumbar veins ([f6]: plate XIV).

**Self-perpetuating widening of FVFI conduits?**

Unusual dilation of the lower end of the sigmoid sinuses was observed mainly in radiographs of patients with a diagnosis of CDMS [6]. It facilitates FVFIs into, or compensatory outflow enhancements from, the related venous periphery and will, in its turn, slowly increase in dependence on the FVFIs’ volume and pressure load. The same circumstances apply to the venous drainages of the spinal canal and await to be considered in future CCSVI or VDMS research.

**Take care**

**CDMS: Offers no random way out**

Neurologists call for CCSVI to be “proven” before its vein stenoses can be treated. The Gold Standard of numbers of hours and months of present or absent neurological dysfunctions which were once convened upon for to identify CDMS is unfortunately not the proper means for “proving CCSVI”. Counting cranial and spinal MRI lesions without regard to specific structural relationships is not of much help either.

**CCSVI is in want of a conceptual consolidation**

The wide spectrum of changeable associations of anomalous structural and functional findings referred to as CCSVI call for its integration into a plausible explanation of related brain and spinal cord lesions. Even if not specific, the lesions’ development in leaps and bounds has to be taken into account. VDMS, being unmistakably defined as a specific condition by a concrete body of post mortem as well as MRI evidence, offers a solid foundation for approaching this goal.

**FVFIs are the missing link between CCSVI and VDMS**

Images of venous impacts damaging the brain and images of a specific overstraining of the spinal cord in line with or between outer fixations find their only plausible explanation in the effects of recurrent FVFIs into brain and spinal canal. CCSVI criterion 2 shows corresponding activities in
the brain, in which criterion 1(a) may play a role. CCSVI criteria 3 to 5 are evidence of important but not always decisive preconditions to the emergence of FVFIs in large neck and prevertebral veins.

**Clinical CCSVI trials: Statistical or rational evaluation?**

The peremptory demand that CCSVI be evaluated but on the basis of its stenoses’ tentative dilations, reasoning exclusively in the domains of clinical trials and evidence-based medicine sidestep the issue that the nature of “(CD)MS” has not been properly defined. Interventions having no clear indication and sound rationale are an undue threat to both patients and interventional radiologists. Is a sink that intermittently overflows best dealt with by exploring means to achieve a statistically significant reduction in the frequency of the unwanted incidents – or by competent plumbing?

**Paying heed to the non-responders’ plight**

Far too many patients with a diagnosis of CDMS, or even one of CCSVI, are not really helped or are even further burdened by the present treatment schemes. Five decades of clinical drug trials on CDMS have hardly improved on these non-responders dismal fate. Only using the best available, and in the future achievable, technology to identify and prevent the FVFIs of VDMS will ease the lot of patients. The first tentative steps in this direction have been made [1, 2, 20, 24].

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