J Neurol (2012) 259:2585–2589
DOI 10.1007/s00415-012-6541-3

ORIGINAL COMMUNICATION

# CCSVI and MS: a statement from the European Society of neurosonology and cerebral hemodynamics

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Received: 29 January 2012 / Revised: 14 April 2012 / Accepted: 30 April 2012 / Published online: 31 May 2012


**Abstract** To systematically review the ultrasonographic criteria proposed for the diagnosis of chronic cerebrospinal venous insufficiency (CCSVI). The authors analyzed the five ultrasonographic criteria, four extracranial and one intracranial, suggested for the diagnosis of CCSVI in multiple sclerosis (MS), together with the references from which these criteria were derived and the main studies that explored the physiology of cerebrospinal drainage. The proposed CCSVI criteria are questionable due to both methodological and technical errors: criteria 1 and 3 are based on a scientifically incorrect application of data obtained in a different setting; criteria 2 and 4 have never been validated before; criterion 2 is technically incorrect; criteria 3 and 5 are susceptible to so many external factors that it is difficult to state whether the data collected are pathological or a variation from the normal. It is also unclear how it was decided that two or more of these five ultrasound criteria may be used to diagnose CCSVI, since no validation of these criteria was performed by different and independent observers nor were they blindly compared with a validated gold-standard investigation. The European

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Society of Neurosonology and Cerebral Hemodynamics (ESNCH) has considerable concerns regarding the accuracy of the proposed criteria for CCSVI in MS. Therefore, any potentially harmful interventional treatment such as transluminal angioplasty and/or stenting should be strongly discouraged.

**Keywords** CCSVI · Ultrasound · Multiple sclerosis

## Introduction

Multiple sclerosis (MS) is an inflammatory, neurodegenerative disease of the central nervous system (CNS) believed to be triggered by an autoimmune attack on myelin. The mechanisms that initiate this attack are, however, unknown [1–4]. A pathophysiological mechanism defined "chronic cerebrospinal venous insufficiency" (CCSVI) was recently proposed by Zamboni and colleagues as a possible cause of MS [5, 6]. According to this hypothesis, abnormal cerebrospinal venous drainage due to extracranial venous obstruction of the internal jugular and/or azygos veins [7] causes a venous reflux followed by blood–brain barrier breakdown, perivenous iron deposition and inflammation in the CNS. However, many subsequent studies have failed to support this hypothesis [8–11]. Despite the lack of scientific evidence to support this hypothesis, Zamboni and colleagues have suggested that unblocking the extracranial venous obstruction using angioplasty can improve the symptoms of MS and reduce relapses. This treatment has been called "the liberation procedure" [12]. Although this proposal was based on the results of a small, non-randomized, non-blinded trial [13], and there have been several reports of complications with this procedure (thrombosis, serious bleeding, stent displacement, re-stenosis, cardiac arrhythmias, and even death) [14], CCSVI has gained a considerable amount of attention worldwide [15].

## CCSVI and ultrasound

The diagnosis of CCSVI is based on five ultrasonographic criteria (Table 1), four extracranial and one intracranial [16].

**Table 1** Ultrasound CCSVI criteria

1. Reflux ($t > 0.88$ s) in the IJVs and/or in the VVs in sitting and supine position
2. Reflux ($t > 0.5$ s) in the DCVs
3. High-resolution B-mode evidence of proximal IJV stenoses (CSA $\leq 0.3$ cm$^2$)
4. Flow not Doppler-detectable in the IJVs and/or VVs despite numerous deep inspirations with the head at 0° and +90°
5. Reverted postural control of the main cerebral venous outflow pathways: negative ΔCSA in the IJV

*CSA* cross-sectional area of the internal jugular vein, *IJV* internal jugular vein, *VV* vertebral vein, *DCVs* deep cerebral veins, $\Delta CSA = CSA_{sitting} - CSA_{supine}$

According to Zamboni's initial findings the presence of at least two of these criteria provides indirect evidence of impaired cerebral venous drainage and should be consistent with the diagnosis of MS. However, the publication of these CCSVI criteria has raised many questions and several independent studies failed to reproduce the detection rates reported by Zamboni. Therefore, a critical scrutiny on the validity of each of these five criteria is mandatory.

1. For the first criterion, Zamboni et al. [7] used the threshold value of 0.88 s to discriminate internal jugular vein (IJV) and vertebral vein (VV) physiological back flow due to valve closure from pathological reflux without performing the Valsalva maneuver (VM) and they found that 71 % of MS patients had a pathological reflux versus 0 % of controls. However, this threshold value comes from a totally different study on IJV valve insufficiency during a controlled VM [17], where it was chosen to differentiate VM-induced insufficiency through insufficient valves lasting >1.23 s, from physiological backward flows during normal valve closure, lasting 0.22–0.78 s. In this study it was found that about 30 % of normal subjects have a physiological ($t < 0.88$ s) back flow during normal valve closure. Furthermore, the utilization of this threshold by Zamboni for assessing reflux in vertebral veins, other than IJV valve insufficiency, is also scientifically incorrect. Finally, the presence of a reflux >0.88 s in the internal jugular vein is more likely to indicate IJVI rather than MS.
2. For the second criterion, the intracranial veins and sinuses were not examined through the transtemporal bone window for which there are published ultrasound criteria and velocity data [18, 19]. Zamboni et al. [7, 16] used a new bone window (supracondylar) for which there are no accepted published criteria nor normative data, and the figures published are not compatible with normal anatomy. With regard to cerebral venous reflux, they found this in 61 % of MS

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patients; however, this evaluation requires a Doppler spectrum analysis, because a color-based approach is inadequate and can easily lead to the misinterpretation of flow direction. More importantly, the rationale of adopting a threshold value of 0.5 s to discriminate pathological reflux in the deep cerebral veins is unclear. This value was derived from studies in the veins of the leg where it served to quantify venous valve insufficiency following deflation of a tourniquet [20, 21]. The rationale for transferring this value from the legs to the brain is very questionable since it has never been validated for deep cerebral veins. The validity and significance of data collected by this method is, therefore, unclear especially if it is used to diagnose CCSVI, where cerebral reflux is not described by the same author as associated with valve incompetence.

3. The third criterion defines a proximal stenosis of the IJV as a cross-sectional area (CSA) in the recumbent position $\leq 0.3$ cm$^2$ [7]. This cut-off value was derived from a study on intensive care patients [22], with possible confounders such as mechanical ventilation and hypovolemia. It can, therefore, not be used as a reference point in healthy subjects. Furthermore, the

**Table 2** Limitations of CCSVI criteria

| | |
|---|---|
| Reflux ($t > 0.88$ s) in the IJVs and/or in the VVs in the sitting and supine positions | 1. This threshold value for the reflux comes from a totally different study on IJV valve insufficiency (IJVI) |
| | 2. The presence of a reflux >0.88 s in the IJV is more likely to indicate IJVI rather than MS |
| | 3. The utilization of this threshold for assessing reflux in VV, other than IJVI, is also scientifically incorrect |
| Reflux ($t > 0.5$ s) in the DCVs | 1. Serious methodological problems: a new bone window (supracondylar) was used for which there are neither accepted published criteria nor normative data |
| | 2. The evaluation of an intracranial reflux requires a Doppler spectrum analysis since, a color-based approach is inadequate and can easily lead to the misinterpretation of flow direction |
| | 3. The threshold value of 0.5 s to discriminate pathological reflux in the deep cerebral veins was derived from studies of the veins of the leg where it served to quantify venous valve insufficiency following deflation of a tourniquet. |
| High-resolution B-mode evidence of proximal IJV stenosis (CSA $\leq 0.3$ cm$^2$) | 1. This cut-off value, derived from a study on intensive care patients with possible confounders such as mechanical ventilation and hypovolemia, cannot be used as a reference point in healthy subjects |
| | 2. It is difficult to decide where to measure the diameter of the veins since IJVs are normally tortuous and the most proximal and distal parts near the superior and inferior bulb are physiologically dilated more than others |
| | 3. Potential pitfalls: even mild pressure exerted by an ultrasound probe or by a contraction of the cervical musculature itself can alter the diameter of the veins leading to false-positive results |
| Flow not Doppler-detectable in the IJVs and/or VVs despite numerous deep inspirations with the head at 0° and +90°. | 1. A lack of flow is not necessarily due to an obstruction since it can occur in the supine position at least in one IJV in healthy subjects. In the upright position, there is a dramatic reduction and frequently a complete cessation of blood flow in the IJVs. In the supine position there also may be no flow in the VVs |
| | 2. An inadequate setting of ultrasound indices such as pulse repetition frequency might lead to an apparent absence of color-coded signals and a misinterpretation of no-flow |
| Reverted postural control of the main cerebral venous outflow pathways: negative ΔCSA in the IJV | 1. In normal subjects, subtracting the CSA measured in the supine position from that in a sitting position (ΔCSA) is usually negative and not a pathological finding |
| | 2. Potential pitfalls: even mild pressure exerted by the ultrasound probe or by a contraction of the cervical musculature itself can alter the diameter of the veins leading to false-positive results |

*CSA* cross-sectional area of the internal jugular vein, *IJV* internal jugular vein, *IJVI* internal jugular valve insufficiency, *VV* vertebral vein, *DCVs* deep cerebral veins, $\Delta CSA = CSA_{sitting} - CSA_{supine}$

original authors [22] still reported a CAS $\leq$0.3 cm$^2$ in 20% of their patients. It is difficult to decide where to measure the diameter of the vein since IJVs are normally tortuous and the most proximal and distal parts near the superior and inferior bulb are physiologically dilated more than others. It is important to stress that even mild pressure exerted by the ultrasound probe or by a contraction of the cervical musculature itself can alter the diameter of the vein leading to false-positive results.

4. The fourth criterion which is the inability to detect flow in the IJVs and/or in the VVs during deep inspiration, according to Zamboni et al. [7], provides indirect evidence of venous obstruction. This criterion has never been validated. In the original paper flow was assessed at rest, rather than during deep inspiration, and this finding was never discussed in the context of venous obstruction [23]. Moreover, a lack of flow is not necessarily due to obstruction since it can occur, e.g., at 15° in both IJVs in healthy subjects [19]. In the upright position, there is a dramatic reduction and frequently a complete cessation of blood flow in the IJV. In the supine position there may also be no flow in the VVs [20]. Furthermore, an inadequate setting of ultrasound indices such as pulse repetition frequency might lead to an apparent absence of color-coded signal and a misinterpretation of no-flow.
5. The fifth criterion examines the presence of a physiological shift of cerebral venous drainage from the jugular venous system to the vertebral plexus with postural change: from the supine to the sitting position. In normal subjects, subtracting the CSA measured in the supine position from that in a sitting position ($\Delta$CSA) is usually negative [19]. Instead, Zamboni wrongly considered that a negative $\Delta$CSA value would represent a reverted postural control of the main cerebral venous outflow pathways [7]. Furthermore, similarly to criterion three, a mild pressure exerted by the ultrasound probe or by a contraction of the cervical muscles may alter the diameter of the vein possibly leading to false-positive results. A more correct method would be to calculate the difference of blood flow (CSA $\times$ velocity) in the two positions (supine and sitting) as has been recently performed not confirming the hypothesis of Zamboni and co-workers [8].

A very important issue is the cut-off point of these criteria to diagnose CCSVI. In fact, it is unclear how Zamboni decided that two or more of the five ultrasound criteria may be used to diagnose CCSVI. Diagnostic criteria using a new alternative method (i.e., ultrasound) are usually compared with a validated gold-standard investigation (venography according to Zamboni et al.). However, Zamboni and colleagues' comparison of venography in 65 CCSVI ultrasound-positive MS patients was not blinded and is, therefore, open to bias. There was also no validation of the CCSVI criteria by different and independent observers. Finally, consequent studies using MR venography could not confirm differences regarding cerebrospinal drainage in MS patients and controls [24–27].

## Conclusion

To this day, a scientifically sound validation of each of the five criteria proposed by Zamboni for the diagnosis of CCSVI is lacking, not to mention their combined application. On the other hand, there is growing evidence [28–31] which rejects the role of CCSVI in the pathogenesis of MS and which suggests that the proposed CCSVI criteria are questionable due to both methodological and technical errors (Table 2). Ultrasound investigation of intracranial and cervical veins is highly operator dependent owing to the wide anatomic and physiological variability of these vessels. Therefore, a study of cerebral venous drainage requires very experienced neurosonographers. Moreover, blinding algorithms are mandatory in assessing MS patients especially during venographic verification of ultrasound findings; these were completely omitted in Zamboni's studies. More accurate ultrasound parameters to determine cerebrospinal venous drainage in MS and in healthy subjects are, therefore, warranted.

The European Society of Neurosonology and Cerebral Hemodynamics (ESNCH) has, therefore, considerable concerns regarding the accuracy of the proposed criteria for CCSVI in MS [7]. We unanimously believe that any potentially harmful interventional treatment such as transluminal angioplasty and/or stenting should be strongly discouraged. This is due, not only to the lack of any evidence, but also to the risk of serious complications for the patients.

**Conflicts of interest** All authors report no disclosures.

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