

## How to objectively assess jugular primary venous obstruction

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### Abstract

Last January *The Lancet* published the article by Traboulsee *et al.* *Prevalence of extracranial venous narrowing on catheter venography in people with multiple sclerosis, their sibilings, and unrelated healthy controls: a blinded, case control study.* These Authors confirmed the presence of chronic cerebrospinal venous insufficiency with a high prevalence of about 70% in the Canadian population, but without significant differences between patients and healthy controls, yet. However, they used a criterion never published to assess stenosis, in alternative to the classic measurement of the diameter in the segment immediately preceding the narrowest point. Traboulsee *et al.* measure the stenosis along the entire length of the internal jugular vein, by comparing the maximum diameter with the narrowest point. It has been demonstrated, from normal anatomy findings, how the jugular bulb diameter normally exceeds 50% of the minimum diameter of the internal jugular vein, clearly showing the reason why Traboulsee *et al.* did not find significant differences between people with multiple sclerosis, their sibilings, and unrelated healthy controls.

Furthermore, as the outcome measure of Traboulsee *et al.*, wall stenosis is a neglected part of primary venous obstruction, because in the majority of cases obstruction is the consequence of intraluminal obstacles, as a considerable part of truncular venous malformations, and/or compression; rarely of external hypoplasia. Finally, several recently published methods can be adopted for objective assessment of restricted jugular flow in course of chronic cerebrospinal venous insufficiency, by the means of non invasive magnetic resonance imaging, ultrasound and plethysmography.

This may help us in improving the assessment of cerebral venous return in the near future.

### Introduction

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the article *Prevalence of extracranial venous narrowing on catheter venography in people with multiple sclerosis, their sibilings, and unrelated healthy controls: a blinded, case control study*, by Traboulsee *et al.*<sup>1</sup>

In that particular circumstance, I felt constrained to reply to Traboulsee and colleagues, because the article repeatedly cites me personally, making comparison with the data published by my group.

In the name of a transparent scientific debate, I prayed the Editor to publish my comment letter to the article, last October 16, 2013.

The article of Traboulsee *et al.* was subsequently published last January,<sup>1</sup> and approximately 2 weeks later the senior Editor of *The Lancet* communicated me to refuse my reply letter. I am still surprised of the editorial decision either because does not permit me to reply despite the article cites me personally, or

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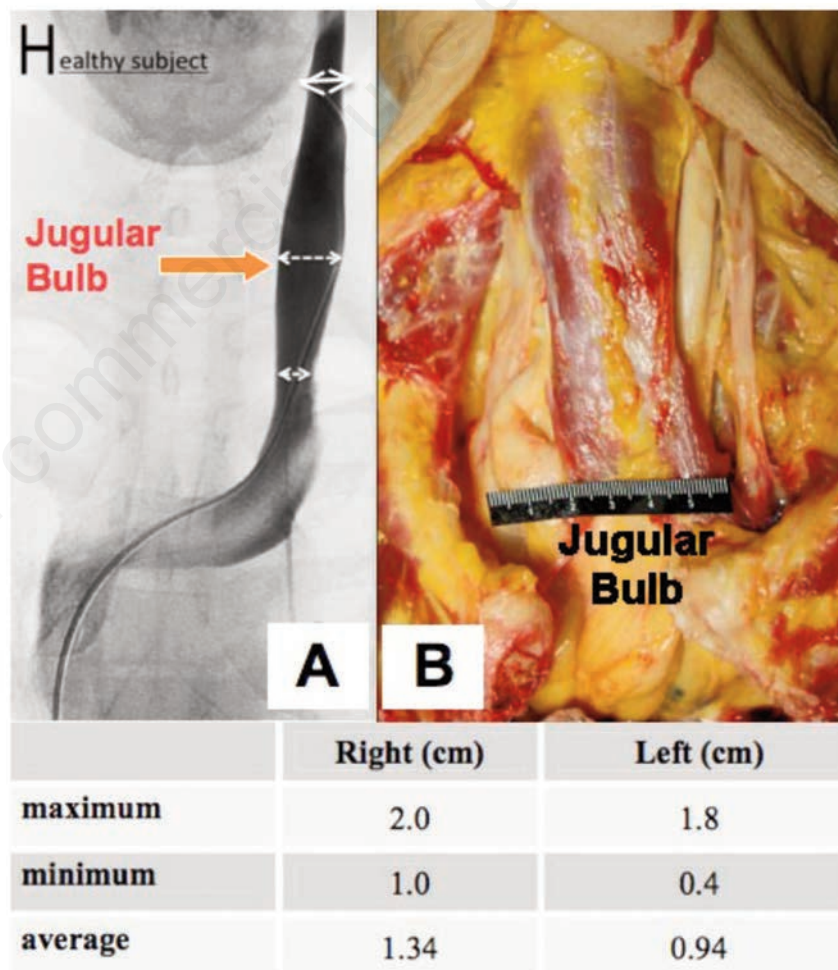


Figure 1. A) Healthy subject catheter venography of the left internal jugular vein (IJV), showing how in normal condition, the jugular bulb exhibits a diameter more than double respect the junction (courtesy of R. Galeotti, MD); B) Autoscopic study showing the dilation of the jugular bulb respect to the other segment of the IJV. The table illustrates the average diameter variation measured in an autoscopic study modified from Furukawa *et al.*, 2010<sup>2)</sup>.

because the Traboulee paper presents various scientific inaccuracies that need to be clarified for the benefit of the scientific community.

The Editor simply stated that asked to the Authors to reply me directly. However, eleven months later I did not receive any reply from the Authors. On the other hand, on the bases of the Lancet article, two comments have been published,<sup>2,3</sup> aimed to close rapidly *the curtain* on the chronic cerebrospinal venous insufficiency hypothesis, despite 13 out of 19 prevalence studies and 3 meta-analysis papers testifies confirming data.<sup>4</sup>

## The concept of primary venous obstruction

Truncular venous malformations (TVMs) are the result of vascular trunk developmental defects occurring during the embryogenesis later stage. When TVMs cause a primary venous obstruction, the latter can be subdivid-

ed in intraluminal obstacles (septa, webs, fixed and rudimental valves) or in wall stenosis (hypoplasia, agenesis).<sup>5</sup>

For instance, among TVMs, May-Thurner syndrome is the consequence of a combination of luminal defect with external compression, whereas primary Budd-Chiari is characterized by membranous obstruction.<sup>6-8</sup>

Whenever TVMs are localized in the internal jugular (IJV) and azygous vein (AZY), a condition known as chronic cerebro-spinal venous insufficiency (CCSVI) follows.<sup>1,4,5</sup>

Quite recently, by the means of catheter venography, in a well designed study, Traboulee *et al.* confirmed the elevated prevalence of venous narrowings in patients with multiple sclerosis. But at the same time, the authors identified this anomaly also in the control population in the same proportion.<sup>1</sup>

To us, this is not surprising because they measured the stenosis by means of a novel criterion that is not quoted into the reference list.

They assessed a greater than 50% wall stenosis by comparing the widest diameter of the vein with the narrowest one, along the

entire vessel length, at any point.

IJV caliber variations have been described by anatomical studies since a long time, together with the presence of a superior and inferior bulb of the same vein. Autopsy evaluations on natural death cases have already demonstrated how the IJV diameter can range from a minimum of 1 cm to a maximum of 2 cm (thus a variability that is greater than 50%) on the right and from 0.4 cm to 1.8 cm (once again greater than 50%) on the left side.<sup>9</sup>

This is well apparent in Figure 1.<sup>9</sup> The region of the bulb is a dilation area of the IJV, naturally presents in the human beings. Even normal IJV show significant caliber variation, by comparing the bulb with for example J3 or J1 segments.

Furthermore, Figure 2 highlights the coronal diameter in the widest and narrowest tracts, showing how variations bigger than 50% can equally occur both in the physiological (Figure 2A) and in the pathological (Figure 2B) conditions.

Thus, by means of the adopted criterion of measuring stenosis >50%, Traboulee *et al.* confirmed the data of the anatomical IJV caliber variability, rather than providing an assessment to discriminate among healthy and pathological cases.

This suggests the possible bias coming out whenever considering the IJV narrowing respect to the maximum diameter along the entire vein trunk the only investigation endpoint. For instance, in our seminal paper, we considered primary venous obstructions from luminal obstacles, as depicted in Figure 2B, as stenosis  $\geq 50\%$ , of course.<sup>10</sup>

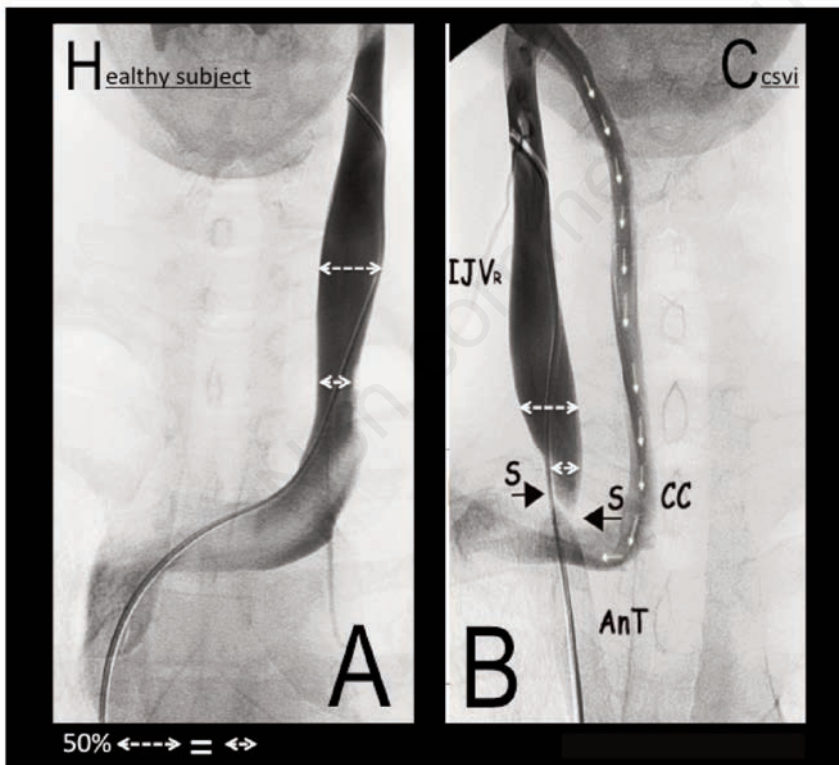
Anyway, as above stated, primary venous obstruction is something else than just a narrowing of the wall. In the vast majority of CCSVI patients, the venous drainage impairment comes as a consequence of intraluminal obstacles (Figure 2B).<sup>5,10-12</sup>

CCSVI latest investigations demonstrate luminal obstacles in 85% of AZY, 50% of right IJV, and 83.3% of left IJV by means of intravascular ultrasound.

Interestingly, in the same population, catheter venography assessed stenosis of  $\geq 50\%$  just in 50% of AZY, 55% of right IJV, and 72% of left IJV.<sup>13</sup>

External compression is also possible in CCSVI, either isolated or in combination, and easy to demonstrate by the means of ultrasound, but never detected by Traboulee *et al.*, yet.<sup>14,15</sup>

In our papers, measuring the stenosis by comparing the narrowest tract with the diameter of the immediately preceding segment, as well as a careful evaluation of intraluminal obstacles and compressions, contributed to a better discrimination of CCSVI cases from controls.



**Figure 2.** Healthy subject (HS) catheter venography (CV) of the left internal jugular vein (IJV). A) The particular shape and caliber variability is well apparent in normal condition. B) Chronic cerebro-spinal venous insufficiency (CCSVI) patient CV of the IJV demonstrating complete obstruction of the lumen by a septum (without any narrowing) (black arrows) that leads to a collateral circle activation to by-pass the obstacle (white arrows). In A) and B) the shorter double tip arrow indicates the narrowest tract, the longer one highlights the vein segment presenting a coronal diameter twice as long as the shorter one. AnT, anonymous trunk; S, septum; CC, collateral circulation (courtesy of R. Galeotti, MD).



## Perspectives

The paper of Traboulsee testifies the lack of standards to objectively measure the restricted brain outflow characterizing CCSVI. A multimodal diagnosis has been recently proposed in a position statement of the International Society for NeuroVascular Disease (ISNVD), indicating a group of invasive and non invasive tests giving comprehensive and complementary information leading to a final CCSVI diagnosis.<sup>16</sup> The multimodality diagnostic system includes ultrasound, magnetic resonance (MR) venography, catheter venography, and intravascular ultrasound. It is likely the most accurate, but too expensive solution. For the reasons above, an inexpensive and non invasive screening method is highly desirable. From this point of view cervical plethysmography, though the accuracy might be further improved, seems a promising first level approach.<sup>17</sup>

Second level examination might rely upon non invasive and objective parameters derived from ultrasound and/or MR imaging. Indeed, new methods objectively assessing cerebral venous outflow by these methodologies have recently been developed.<sup>18-21</sup>

Finally, we need of an accurate third level of investigation. We may agree that the final decision about the surgical approach should be founded on more objective evaluation through catheter venography. Quite recently Veroux *et al.* overcome the difficulty linked with the lack of knowledge about rate of stenosis and normality of venograms. They introduced the concept of the clearance time of the contrast dye when injected in the veins by a standardized and reproducible protocol. These Authors calculated in a group of healthy controls that a standardized injection of contrast dye is eliminated in less than 2 s through the IJV.

The Authors measured the clearance time also in a huge group of CCSVI patients, found a significantly increased time of elimination in about 80% of the examined IJVs. I hope that this methodology, highly objective and reproducible, could be rapidly spread and adopted for endovascular procedures on the IJVs.<sup>22</sup>

Despite the Traboulsee' paper, all the above recent references as well as the ISNVD position paper testify that the scientific debate is alive and continues. It's a regret that the group of Traboulsee did not find these arguments interesting and at least worthy of a personal response.

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