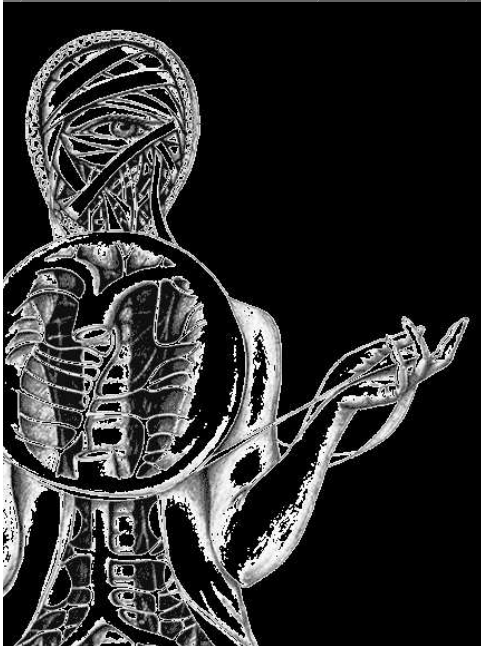


CHRONIC CEREBROSPINAL VENOUS INSUFFICIENCY AND MULTIPLE SCLEROSIS: THEORETICAL AND PRACTICAL ISSUES



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MS and CCSVI

- Multiple sclerosis has been for years considered as a primarily autoimmune disease of as yet undetermined etiopathogenesis.
- Yet, recent findings by Prof. Paolo Zamboni indicate that multiple sclerosis and stenocclusions in the veins draining the brain and spinal cord (so called chronic cerebrospinal venous insufficiency: CCSVI) seem to be two sides of the same coin, with CCSVI being the phenomenon indispensable for the development of multiple sclerosis



MS and CCSVI

- **QUESTION:** could such venous lesions be responsible for the development of MS
(since one may argue that patients who develop thrombosis of the internal jugular veins or have their jugular veins removed due to neck cancer, do not suffer from multiple sclerosis)
- **ANSWER:** MS is a slowly progressing pathology, and it takes at least 10-20 years to develop fully symptomatic disease, while early clinical signs of MS, like headaches and visual disturbances are also seen in patients with thrombosed or excised jugular veins



MS and CCSVI

- ◎ **MORE ARGUMENTS:**
patients with **dural arteriovenous fistulas**, and with **neuro-Behçet disease** (both pathologies are associated with **impaired venous outflow** from the brain and spinal cord) develop lesions alike **MS**
- ◎ Thus, it seems likely that **venous lesions** depicted by professor Zamboni could be responsible for the formation of **MS plaques**



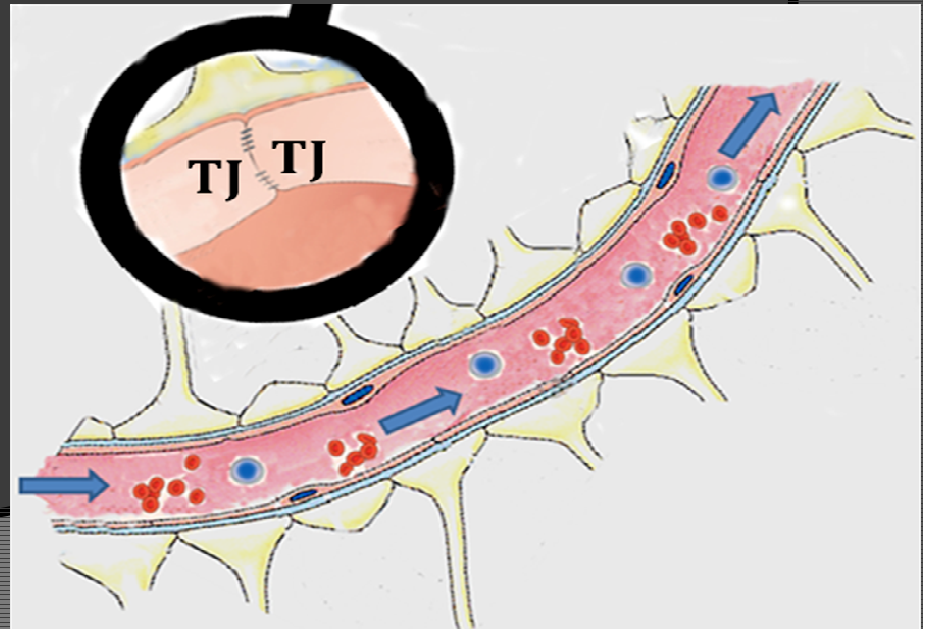
MS and CCSVI

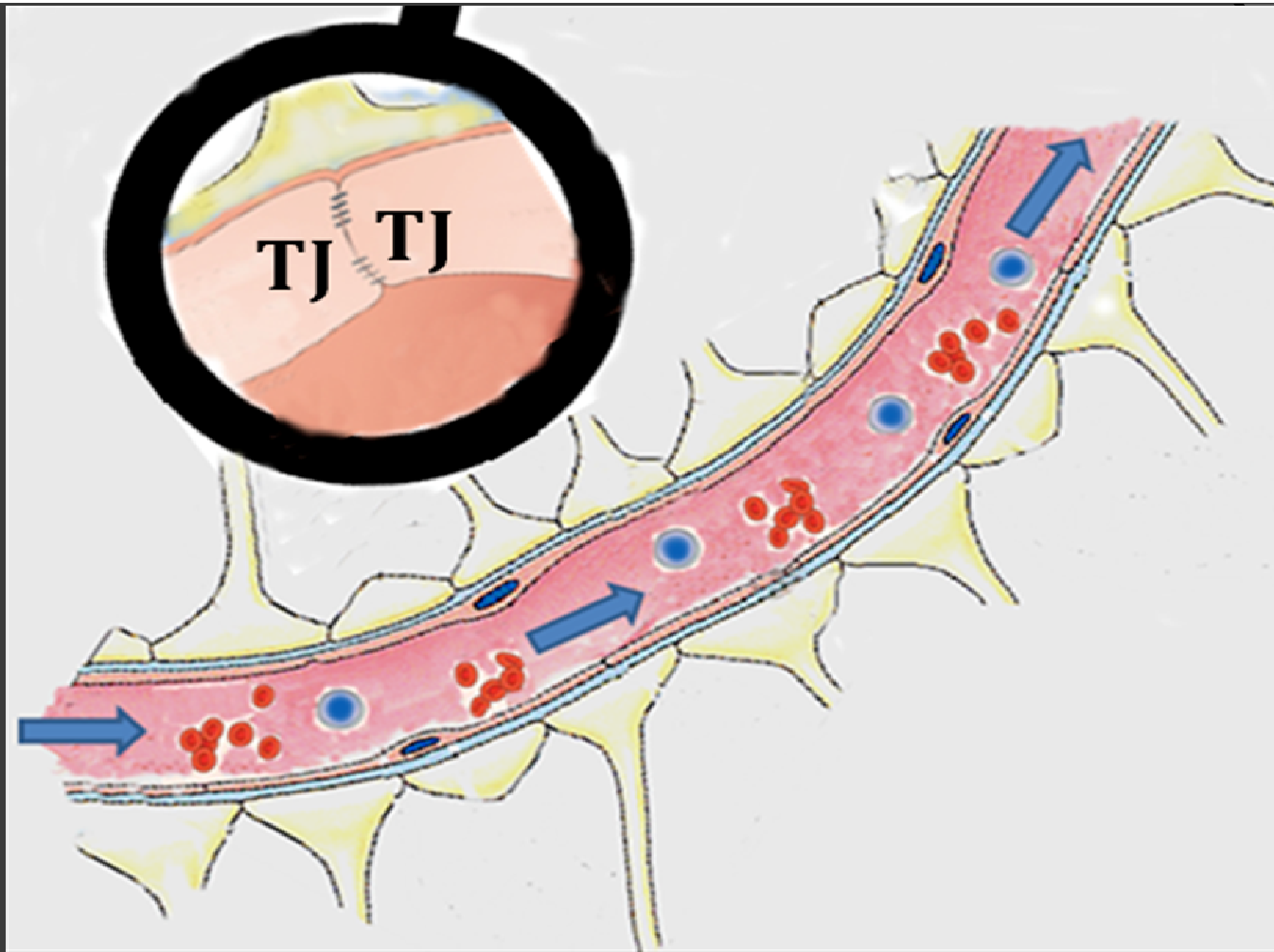
- ◎ **QUESTION:** Which mechanisms in particular might be responsible?
- ◎ **ANSWER:** We have no clear answer at the moment, yet - such a mechanism could share some properties with the **chronic venous insufficiency** in the lower extremities, that results in the development of venous ulcers



MS and CCSVI

- At normal conditions nervous tissue is separated from the blood by a strong, nearly impermeable barrier that is built by cerebrovascular endotheliocytes and their highly specialized interconnections, so called tight junctions



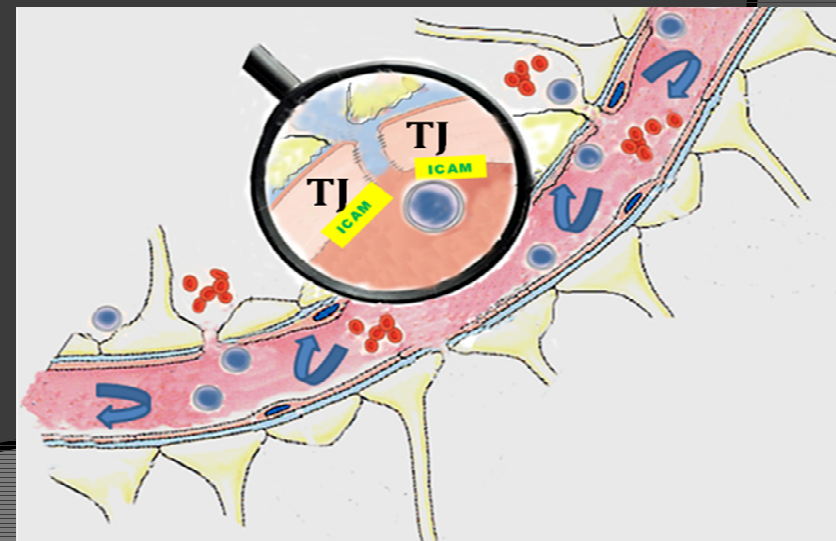


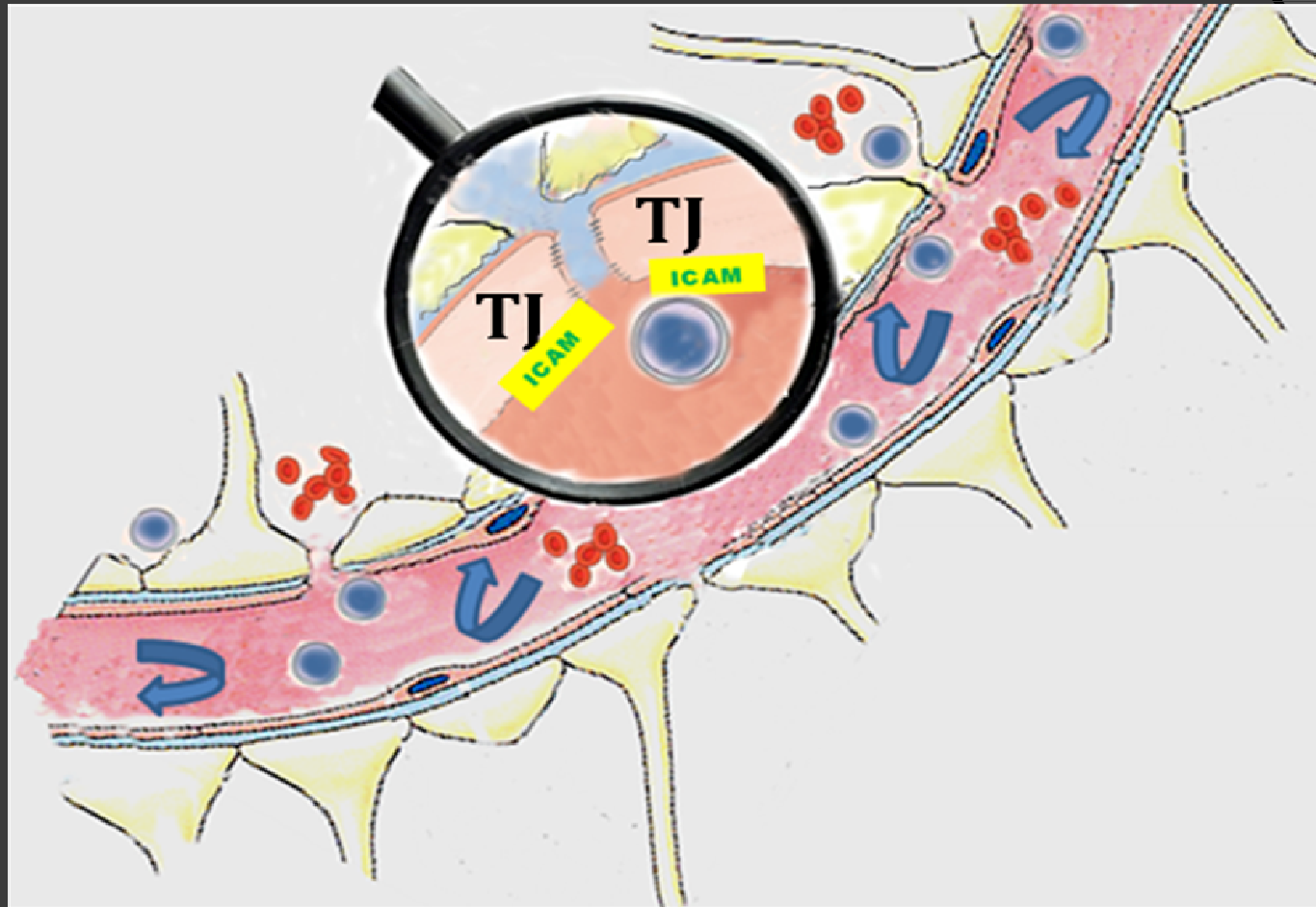
under steady flow tight junctions build the strong barrier, which does not allow blood components, like erythrocytes or immune cells to penetrate the nervous parenchyma



MS and CCSVI

- The integrity of the blood-brain barrier is dependent on many factors, on the level of shear stress in the postcapillary venules in particular





Refluxing flow and venous stasis open tight junction, which leads to the extravasation of erythrocytes, iron storage in the extravascular interstitium, and to the entering of immune cells in close contact with oligodendrocytes (cells building myelin sheaths)



MS and CCSVI

- Breakdown of the blood-brain barrier secondary to the impaired venous outflow from the brain and spinal cord is thought to initiate autoimmunity
- It is an important, yet not the only problem encountered by patients with CCSVI
- **Hypoperfusion** related to venous obstacles appears to be even more important problem



MS and CCSVI

- Recent findings like: results of a long-term treatment of immuno-modulating agents, perfusion MRI studies, and post-mortem studies, indicate that **MS plaques** and **autoimmunity** are actually **a tip of iceberg**, and not the most important pathologies responsible for progressing disability in MS patients.
- Those studies claim for a **neurodegenerative process**, most likely similar to a chronic ischemia, as the main problem in multiple sclerosis.
Yet, until recent discovery by Paolo Zamboni, the factor responsible for this neurodegeneration and ischemia remained elusive.



Brain hypoperfusion secondary to CCSVI

- Thus, in addition to the breakdown of the blood-brain barrier and triggering the autoimmune reaction, venous outflow blockage might be responsible for such pathologic reactions as:
 - ischemia-driven apoptosis of oligodendrocytes
 - ischemia-dependent impaired functioning of neurons
 - ischemia-dependent impaired axonal transport
 - ischemia-dependent glutamate-driven excitotoxicity of neurons and oligodendrocytes



Sonography for the diagnosis of CCSVI

- Since the inflammatory reaction and neurodegeneration seem to progress in the presence of venous obstacles, it looks reasonable to unblock these lesions **as early as possible**, before an **irreversible damage** to the central nervous system develops
- **In this context, sonographic examination seems to be a diagnostic tool of choice, since it is relatively cheap, non-invasive, and widely accessible**



Sonography for the diagnosis of CCSVI

- At the moment, ultrasound scanning for a presence of venous lesions is performed mostly in highly symptomatic MS patients, who are already diagnosed for this disease
- But - in the future - it might be performed also in patients with mild, undetermined symptoms, in order to diagnose CCSVI/MS at its pre-clinical stage and to eradicate most of the highly disabling cases of MS.



Sonography for the diagnosis of CCSVI

- ⦿ Perhaps a substantial percentage of slowly progressing cases of MS, with no overt relapses, is not properly diagnosed at the moment, and is managed as, for example: senile dementia, atherosclerotic neurodegeneration, etc.
- ⦿ **In the future - in such cases a correct diagnosis could be taken and a patient could be properly treated – with no resulting disability**



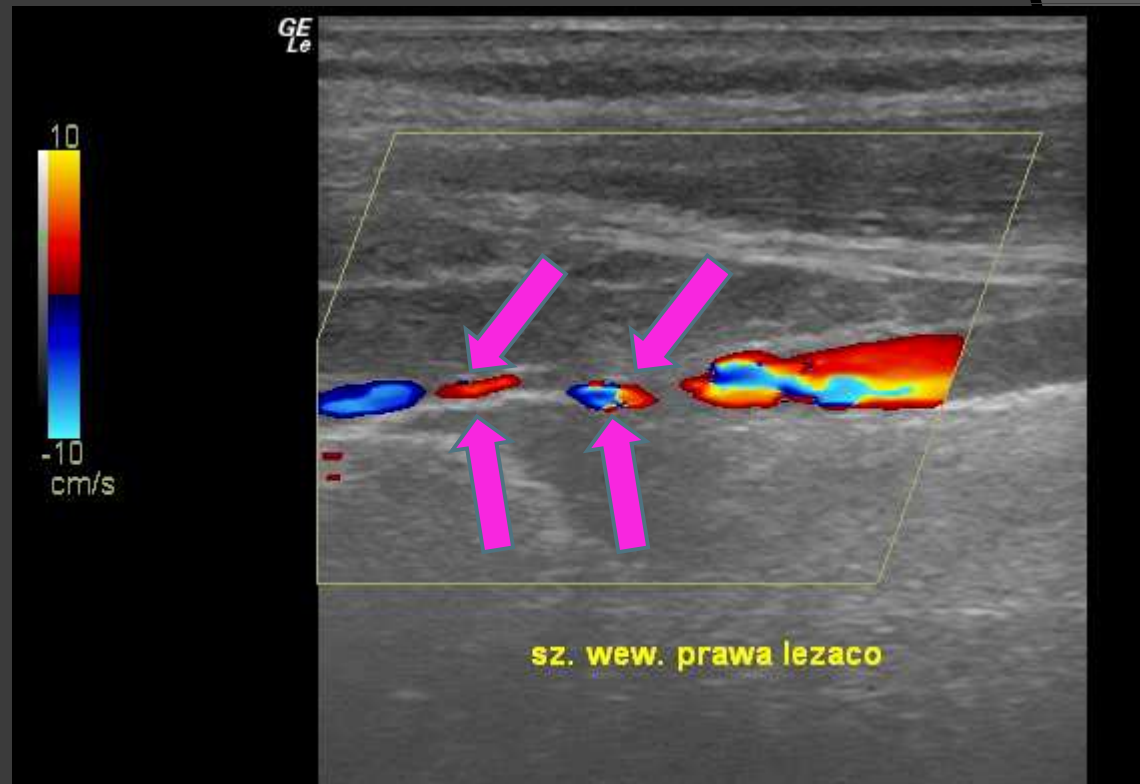
Sonography for the diagnosis of CCSVI

- Sonography gives some advantages to CT and MR venography: apart from anatomic visualisation of a lesion, it gives important information regarding hemodynamics
- It can be performed in both supine and sitting or upright positions, which, in respect to physiology of venous return from the brain, is of critical importance
- Yet, sonographic assessment of the veins draining the central nervous system requires training, experience, and a good sonographic machine
- Such limitations, however, apply also to others non-invasive imaging techniques

Sonography for the diagnosis of CCSVI

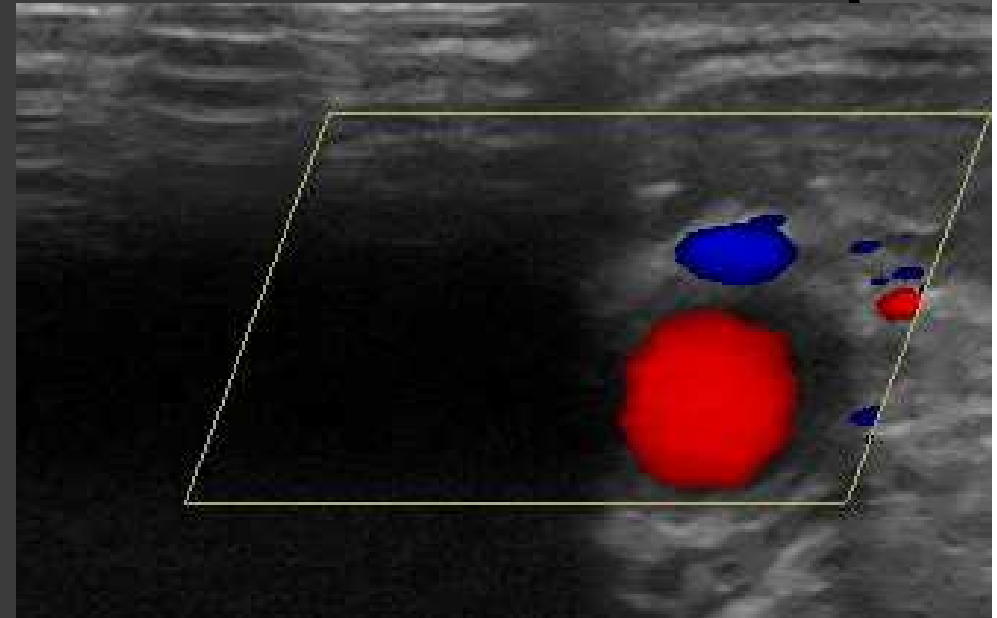
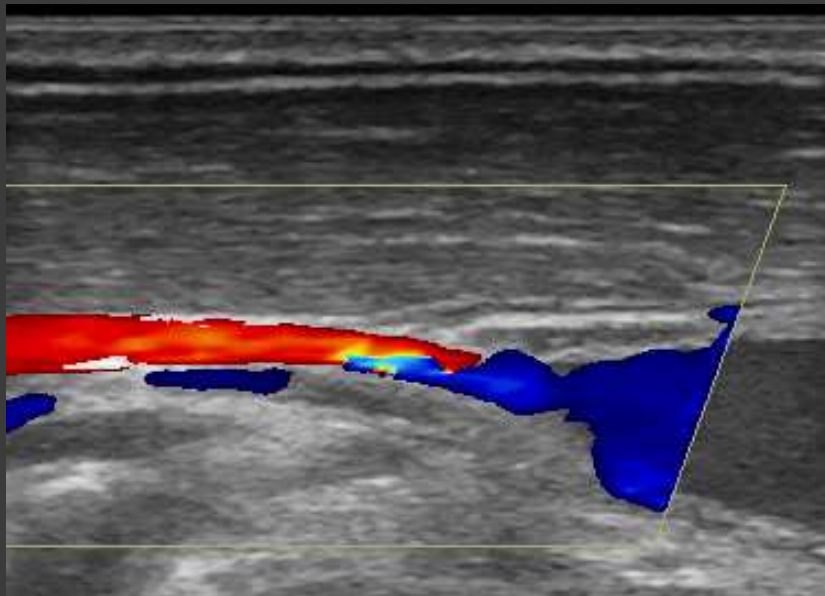
direct visuallization of the lesions

- ⦿ **stenoses**
- ⦿ occlusions
- ⦿ anatomic anomalies like membranes or inverted valves



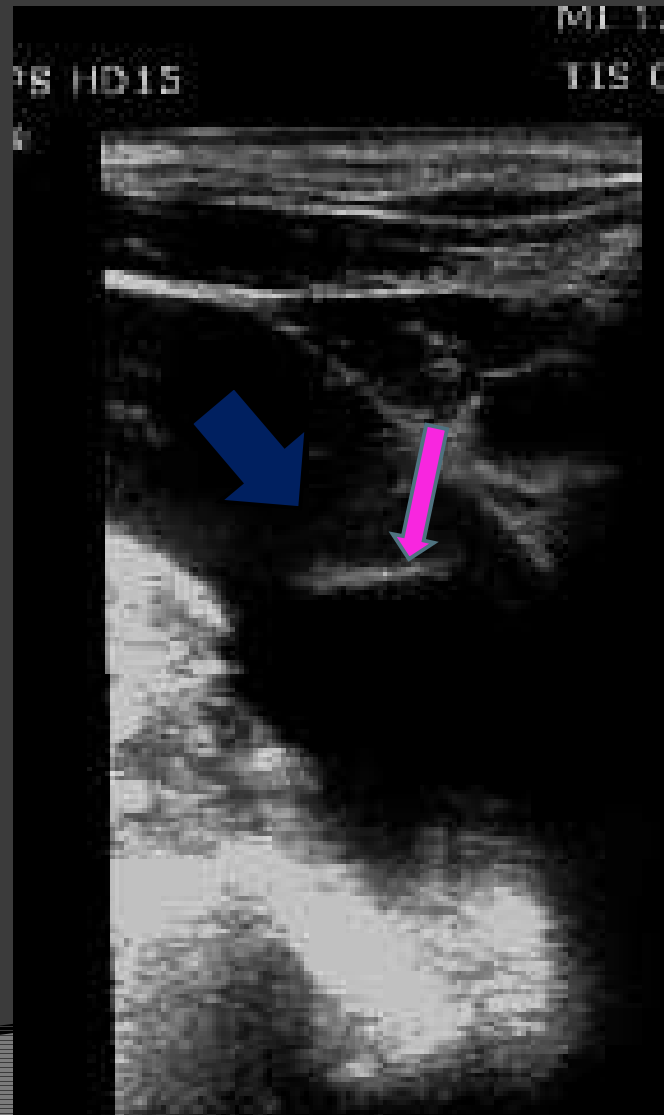
Sonography for the diagnosis of CCSVI

direct visuallization of the lesions



Sonography for the diagnosis of CCSVI

- inverted valve





Sonography for the diagnosis of CCSVI

indirect diagnosis of such lesions

- pathologic refluxes
- no flow or abnormally low flow in a patent vein
- abnormally high flow in vertebral veins in the supine position
- non-compliant internal jugular veins
- refluxes in deep cerebral veins and cerebral sinuses
- collateral venous circulation (vicarious shunts)