Venous valve and cerebral venous system

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It is known that internal jugular vein valve incompetence (IJVVI) leads to retrograde venous flow during Valsalva maneuver (VM) with transient increase of intracranial pressure. Intracranial venous congestion caused by retrograde jugular venous flow might play a role in the pathophysiology of exertional headache with IJVVI as a risk factor.[1] Cough headache is a transient headache upon coughing, bending, stooping or lifting in the absence of intracranial lesions. IJV and vertebral vein (VV) valve incompetence were common findings in benign cough headache (BCH) and BCH might be associated with thoracic inlet valvular incompetence.[2] Jugular venous reflux (JVR) is considered to be involved in the pathogenesis of transient monocular blindness.[3] Venous valve dysfunction is speculated to be the cause of several diseases, but the function of the venous valve is not fully understood. In this review, I examine the relationship between venous valve function and cerebrospinal venous circulation.

History [4]

Aquapendente (1537 -1619), who was a teacher of anatomy at the University of Padua, published "De Venarum Ostiolis" (1603) with a correct description of venous valves. He clearly realized the regulatory function of venous valves and assumed that it was the function of venous valves to "*moderate excessive congestion of blood*".

Galen already had knowledge of cusp-shaped semilunar structures in the lumen of veins.

William Harvey, born on April 1, 1578, in Folkstone at the Channel, published (Wilhelm Fitzer Press, Frankfurt am Main) a small book of 72 pages: "Exercitatio anatomica de motu cordis et sanguinis in animalibus" (Anatomic Treatise on the Motion of the Heart and the Blood in Animals). He clarified the function of venous valves.

-"*It would therefore appear that the function of the valves in the veins is the same as that of the three sigmoid valves which we find at the commencement of the aorta and pulmonary artery, viz., to prevent all reflux of the blood that is passing over them.*"

-"*The veins, in short, as they are the free and open conduits of the blood returning to the heart, so are they effectually prevented from serving as its channels of distribution from the heart.*"

No further comment is necessary to *W. Harvey's* classic statement that the main function of venous valves is to maintain the direction of the blood flow to the heart. For that reason the

number of valves increases distally so that retrograde waves of blood may be stopped

Embryology of Venous Valves

The embryologic development of venous valves was investigated by *Jager* (1926)[5] as well as by *Kampmeierand La Fleur Birch* (1926-1927). In the jugular veins of pig embryos with head-to-coccyx sizes ranging from between 74 and 83 mm, *Jager* found incipient bulgings of the lumen which constitute the preliminary stage of venous valves.

kampmeier and La Fleur Birch [6]studied human embryos. In the region of the sapheno-femoral junction they found the earliest traces of venous valves in embryos at 3.5 months. Towards the end of the fifth month a substantial number of venous valves could be found.

According to Rickenbacher (1966) the valves originate concurrently with the differentiation of the media in the endothelial tubes, which are devoid of any muscular layer up to this time.

Kampmeier and *Birch* divided the development of venous valves into five phases:

1. The first sign of an emerging venous valve is a thickening of the endothelium, which at this stage is largely inconspicuous and forms a pair of ridges placed transversely to the axis of the vessel. When these twin-ridges increase in size and touch each other, a ringlike structure evolves.
2. Invaded by the mesenchyma situated below, the endothelial anlage grows; at the same time the vessel bulges out leeward of the valvular anlage.
3. The evolving valve directs itself toward the lee, the bulge on the upstream side of the valvular anlage increases, the outline becomes crescentic.
4. The valvular sac gains in capacity, the free edge of the valvular cusp widens to nodular shape, an effect which is caused by active involvement of the local mesenchyma.
5. The venous wall thins down considerably in the region of the valvular sinus; this process of thinning occurs mainly at the expense of the media, the remaining thickness of which is only one fifth of that observed in other regions of the vessel. In particular, the circular muscles become weaker. The *thickening* of the cusp margin observed in phase (4) *disappears;* a valve with clear-cut valvular function has come into existence (Fig. 2).

Occurrence and Distribution of Venous Valves

In *animals,* we find venous valves in amphibians, such as frogs *(Suchard,* 1907). In birds venous valves occur less frequently than in human beings; the distribution of venous valves in domestic animals is approximately equal to that in humans *(Ellenberger* and *Baum,* 1908). In his classic novel *"Moby Dick" Melville* (1851) states that whales do not have venous valves. If injured, whales will lose blood extremely fast and in vast quantities.

Williams (1954) made a comparative study on the occurrence of valves in the veins of the extremities of monkeys, dogs and cats. Dogs were found to have the most venous valves, occurring more frequently in the superficial veins than in the deep ones.

According to *Franklin* (1927), valves do not occur in veins with a diameter of less than 1 mm.

Dzillas (1949), however, describes valves in postcapillary veins with diameters from 20 to 145 μm. His findings are fully confirmed by *Spalteholz* and *Rulffs* (1958) as well as by other authors

The first venous valve cranial from the heart is found in the subclavian and internal jugular veins, not far from their confluence, which forms the anonymous vein. These valves have a certain importance in connection with infusion therapy. If the tip of an intravenous catheter is located on the cardiac side of these valves, the valves will close during the infusion, and the infused volume will reach the heart faster than if the application were made more cranially. For that reason, Schaeffer (1973) called these veins "border valves" ("Grenzklappen ").

No valve in the cerebrospinal venous system

The fundamental feature that distinguishes the cerebrospinal venous system from the systemic (caval) venous system is the lack of venous valves. In 1940, Batson[7] demonstrated that the vertebral venous system (VVS) was angiographically connected to the cranial venous system, allowing retrograde flow from the VVS into the brain due to the lack of venous valves. Anderson's[8] experiments in living humans confirmed contrast material injected into the VVS reached intracranial venous sinuses and internal cerebral veins in retrograde fashion. Groen[9] further established the lack of valves and the connection of the vertebral venous plexus with cranial sinuses, subcutaneous cranial veins, intercostal veins, and sacral venous plexus. Later, angiographic studies by Lasjaunias and Berenstein[10] verified retrograde flow into radicular veins and showed retrograde flow into nerve roots, spine, and vertebral bodies. Gisolf's mathematical model[11] predicted increased central venous pressure would result in caudal-to-cranial venous blood flow via the VVS, aligning with Batson's earlier postulation.[7],[12] Thus, retrograde and bidirectional flow are inherent characteristics of all cerebrospinal venous system elements due to the lack of venous valves.[13]

IJV valve

The existence of the IJV valve has been described previously by Harvey in 1941. This plays a role in the prevention of cephalad flow of venous blood.[14] The IJV valves are absent in 6% to 13% more commonly in the left-sided than the right-sided veins. The IJV valves are typically bicuspid valves (66%), but can be unicuspid (15%), tricuspid (6%), or absent (13%).[15] The IJV valves are located at an average distance of 0.3 to 0.5 cm above the junction with the brachiocephalic vein, but the position in the neck or chest can vary from being almost directly posterior, to 3 cm inferior and lateral, to the head of the clavicle. (Fig.3)

Intracranial hypertension

Stenosis of large intracranial venous sinuses can be found in MRV in almost all idiopathic intracranial hypertension (IIH)subjects and are considered a reliable radiologic marker of intracranial hypertension, with a high specificity (93%) and sensitivity (93%). Stenosis may have various conformations. Smooth narrowing of a sinus segment associated or not with definite flow gaps are the most frequent, but segmental hypoplasia or aplasia of one or more central venous collectors, sometimes extended to a whole transverse sinus, can be not infrequently found. Significant transverse sinus calibre asymmetries can be sometimes followed along the jugular veins

of the same side.
In many cases, an instability of brain perfusion autoregulation and/or a jugular valve incompetence may trigger a self-sustained intracranial hypertension in presence of sinus venous stenosis.[16] The prevalence of valvular insufficiency is more than double compared to a control group that was matched for age, gender and BMI.[17] These results support the hypothesis that impeded venous return from the brain may play a causal role in the etiology of IIH.

Transient global Amnesia (TGA)

The vein of Galen provides primary venous drainage for the diencephalon and mesial temporal lobes, the structures involved in TGA.[18] There is an evidence that venous ischemia due to venous hypertension, such as from retrograde venous congestion from AVMs or dAVFs, may induce potentially reversible ischemic changes in the brain, which may involve memory structures. However, there is no proof that transient retrograde venous pressure is associated with cerebral dysfunction. Kurokawa studied cerebral venous hypertension in rats, and NADH fluorescence of brain slices (a sensitive and early indicator of metabolic disturbance) showed metabolic disturbances consistent with venous ischemia after 15 min of venous hypertension by occluding SSS.
Valvular insufficiency may lead to increased venous pressure transmission during a VM and thus contribute to venous ischemia in TGA. On colour-coded duplex ultrasonography, only during the VM was the retrograde flow component significantly more frequent in the TGA group than in the controls (46·7 vs 23·3%).[19] This insufficiency seems to be most likely to arise in the right jugular vein.
The association of valvular insufficiency (VI) and longer reflux times with the occurrence of a trigger event further suggests that cerebral venous congestion is an important etiological factor in TGA. [20] The significantly higher prevalence of IJVVI in TGA patients. However, no specific IJVVI related intracranial venous drainage patterns could be found to further support the hypothesis of a direct causal relation between IJVVI and TGA.[21]
US Investigation confirmed that the total venous flow decreases in the IJVs and vertebral veins of the patients with TGA. IJV drainage is relatively compromised during the VM in the patients with TGA. Using MR imaging, The patients with TGA manifest a higher prevalence of compression/stenosis of the bilateral IJVs and left brachiocephalic vein, and TS hypoplasia, which supports the hypothesized role of abnormal brain venous drainage in the pathogenesis of TGA. [22]

Postural dependency of the cerebral venous flow

Normally, the cerebral venous drainage mainly flows through the IJV in the supine position. In contrast, in the upright position, this drainage mainly flows through the vertebral venous system.[23] (Fig.4) Batson (1940) reported that flow in the vertebral venous plexus is actually reversed (directed in a caudal to cranial direction) during straining. He stated that vertebral plexus flow reversal during straining (such as induced by coughing) offered an explanation for the high incidence of cranial metastases with lung abscess and bronchiogenic carcinoma. Gisolf stated that implementation of vertebral venous valves would not influence the simulations of flow distribution,

because their model does not demonstrate substantial vertebral plexus flow reversal.
From an evolutionary standpoint, as we became bipedal, certain accommodating mechanisms developed to prevent during upright positioning the over-drainage of fluid (CSF or blood) from the cranial to the spinal compartment, which could lead to intracranial hypotension.[24] One such mechanism known as the "Starling resistor," which has been conserved across species. Essentially, the Starling resistor is a mechanism that maintains constant flow through collapsible tubes (such as cortical draining veins) when they are surrounded by variant ambient pressure (CSF in the subarachnoid space) all contained in a rigid box, such as the skull in the hydraulic model shown in Fig. 5.

Vertebral venous valve

In the previous papers, there are descriptions like 'the IJV valve is the only valve between the heart and the brain' that appears to be inaccurate. The vertebral veins serve as important venous vessels for blood returning from the brain. Gray's Anatomy describes how the vertebral veins collect the blood, go through the first to sixth transverse cervical foramina, and finally descend to open superoposteriorly into the brachiocephalic vein. The opening of the vertebral vein has a paired valve. The clinical significance of the vertebral venous valves has not been studied. At the end of the 19th century Poirier still gave an extensive description of the vertebral venous system. He mentioned that the vertebral plexuses can serve as a sufficient collateral pathway for the superior and inferior vena cava and there are valves at certain locations in the vertebral venous system.
Chou CH visualized the two cusps of the valves at the opening of the vertebral vein into the brachiocephalic vein.[25] The synchronization of valvular motion between jugular and vertebral valves is a reasonable finding, because the hemodynamic changes are the same. They raised a question to the general thought that the IJV valve is the only protective venous vessel valve between the heart and the brain.

Vertebral venous plexus

There are vertebral venous plexuses at the craniocervical junction composed of multiple interwoven vessels concentrated anteriorly (anterior vertebral plexuses), posteriorly (posterior vertebral venous plexuses), and laterally (lateral vertebral venous plexuses). [23] Bicuspid valves in 34% of veins sampled from the external vertebral venous plexus were found.
Some have also hypothesized that the vertebral venous plexus may be involved in thermoregulatory regulation and "cooling" of the spinal cord. the anatomy of the IVVP and its connecting veins may serve to thermoregulate the spinal cord and that climate related anatomical adaptations were present in the species studied.[26]
The morphological pattern of the anterior internal vertebral venous plexus (IVVP) in the fetus is very similar with the anterior IVVP in the aged human. (Fig.6) In contrast, the posterior IVVP in the fetus lacks the prominent transverse bridging veins that are present in the aged lower thoracic and the lumbar posterior IVVP. the thoracolumbar part of the posterior IVVP is subject to ''developmental delay,'' or the observed differences in the aged may result from functional and

age-related factors that trigger this part of the vertebral venous system during (erect) life.[27]

Summary

Intervention for cerebral venous diseases, especially in cases related to dural venous sinuses, has been gaining attention. When evaluating cerebral circulation, considering the cerebral venous system is essential. However, the cerebral venous system remains incompletely understood. It is crucial to comprehend not only its role as a pathway from the brain to the heart but how it functions within the cerebral venous system and its impact. This understanding can contribute to effective treatment strategies for cerebral venous and venous sinus disorders.

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Figure

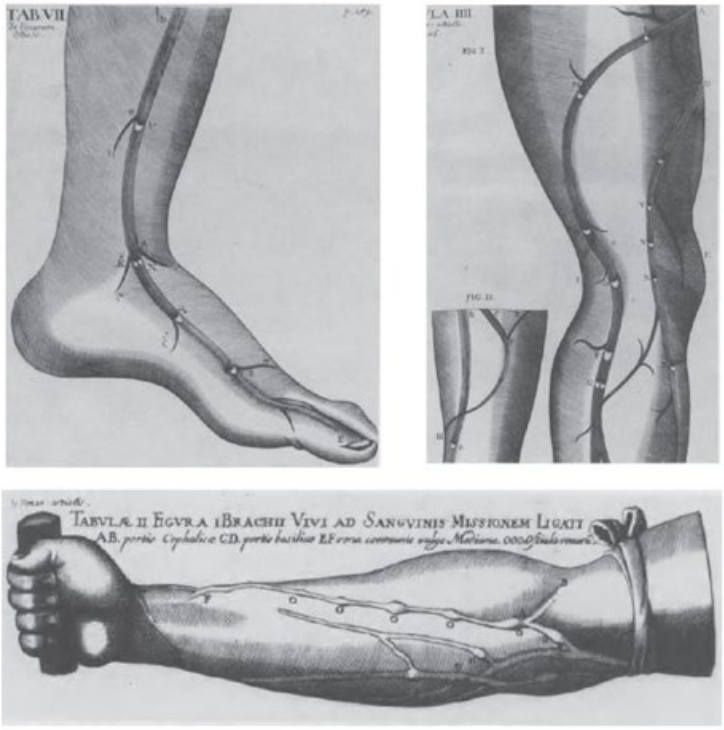

Fig.1
Upper left： Valves of the distal long saphenous vein (from Aquapendente)
Upper right: Valves of a leg vein (from Aquapendente)
Lower： The illustration contained in Harvey's "The motion of the Heart and the Blood".

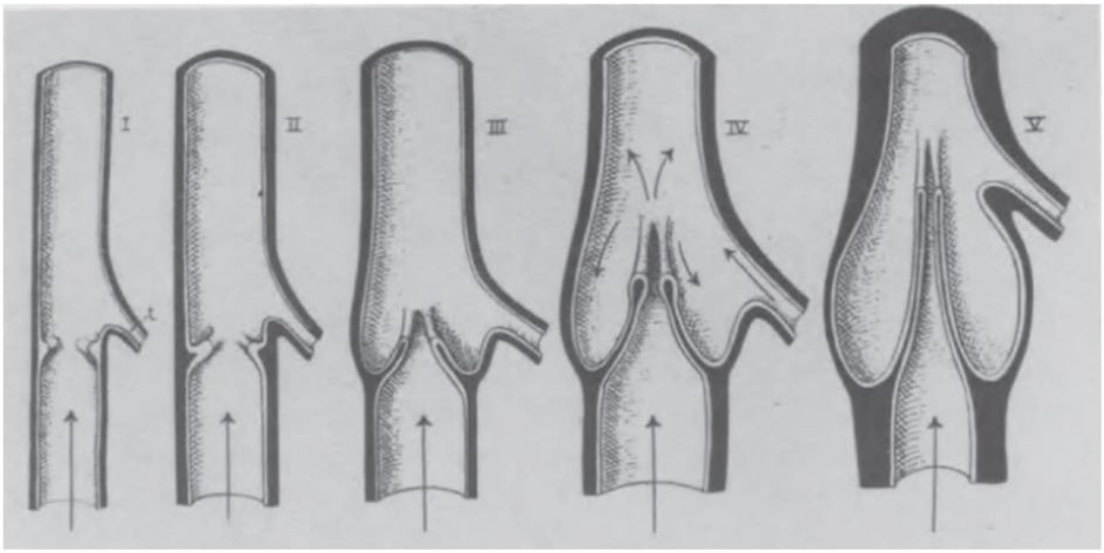

Fig.2 Diagram of the development of a bicuspid valve. *V* state at full term.
(from Kampmeier and Birch, Am J Anat 1936)

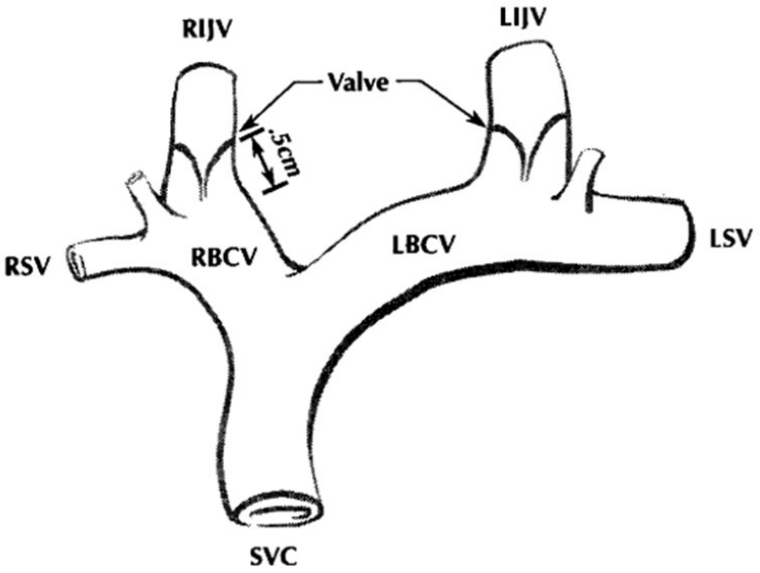

Fig.3 Anatomical diagram of internal jugular valves

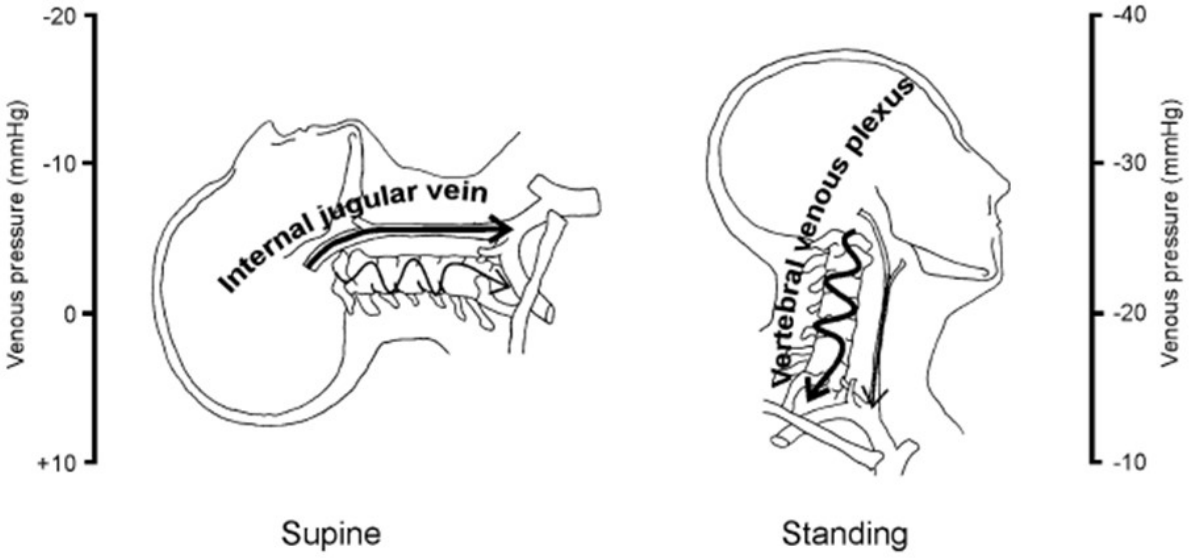

Fig.4 Illustration of the cerebral venous outflow pathways (ref11)
Primarily vie the internal jugular veins in the supine position (left) and the vertebral venous plexus in the upright position (right).

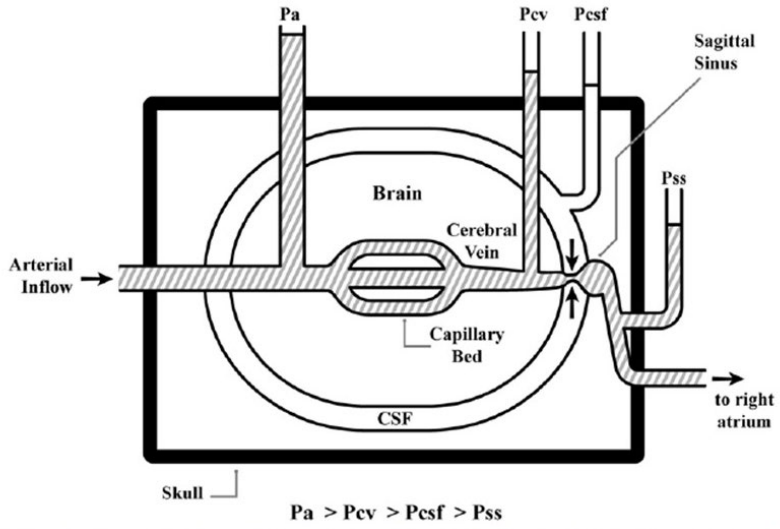

FIG. 1. Schematic of the hierarchy of pressures of various liquid components of the intracranial space. *Arrows* indicate the Starling resistor at the lateral lacunes (the junction between the cortical bridging vein and the sagittal sinus). Arterial inflow pressure (Pa) is higher than CSF pressure (Pcsf), which in turn is higher than pressure in the superior sagittal sinus (Pss). Pressure in the upstream cerebral veins (Pcv) is always maintained above Pcsf because of the constriction effect by the Starling resistor; this phenomenon also prevents venous overdrainage during upright positioning when sagittal sinus pressure falls. From Luce et al: *J Appl Physiol* 53:1496–1503, 1982. Published with permission.

Fig.5
Schematic of the hierarchy of pressures of various liquid components of the intracranial space. (Luce, et al. *J Appl Physiol* 53:1496-1503, 1982)
Arrows indicate the Starling resistor at the lateral lacunes (the junction between the cortical bridging vein and the sagittal sinus).
Pa: arterial inflow pressure, Pcv: pressure in the upstream cerebral veins, Pcsv: CSF pressure, Pss: pressure in the superior sagittal sinus

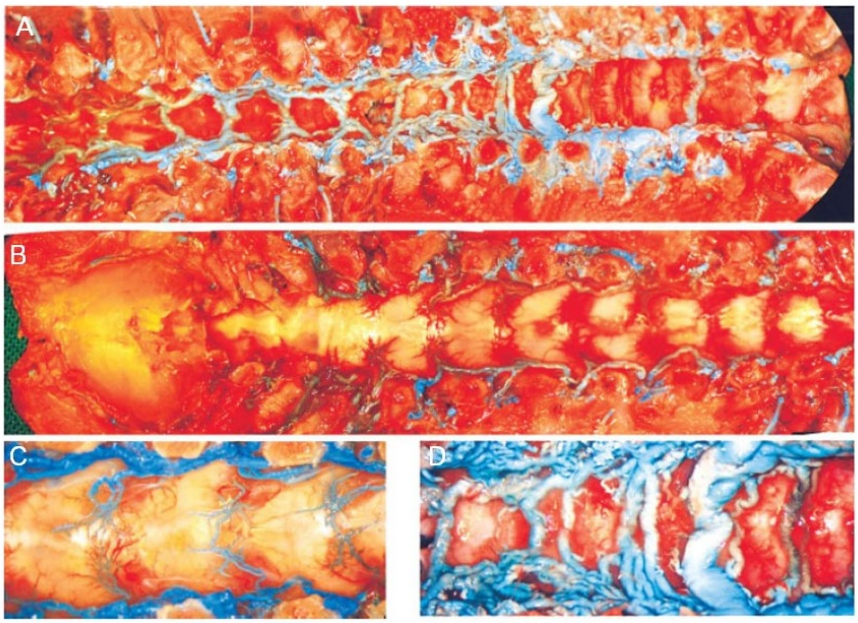

Fig.6 Typical example of the human fetal posterior internal vertebral venous plexus at the cervico-thoracic area (A) and the lumbosacral area (B), with detail of the C6-Th3 area (C) and the lumbar area (D). (ref27)