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The Chronic Stenosis of the Internal Jugular Veins as a Cause of Multiple Sclerosis

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Abstract

Recent perfusion-weighted imaging studies have shown that two clinical pictures characterize multiple sclerosis: intermittent focal inflammatory demyelination and diffuse progressive axonal degeneration. Their etiopathogenesis is not known. We hypothesize that a chronic obstacle to the outflow of blood from the brain can cause these two clinical pictures. We had already shown angiographically that the stenosis of the internal jugular vein causes a systemic-cerebral shunt and a reversal of the venous circulation brain and gives rise to the new circuit that directly connects the superior vena cava system to the straight sinus. This new circuit can cause the BBB to break and new plaques to form.

The introduction of near-infrared spectroscopy (NIRS) in cardiac surgery has made it possible to demonstrate that obstruction of the superior vena cava is capable of causing cerebral hypoperfusion, responsible for the progressive degeneration of axons.

To confirm the relationship between superior vena cava syndrome and cerebral hypoperfusion, in 35 of the152 patients with multiple sclerosis (MS) and jugular vein stenosis, operated on the plastic of jugular vein enlargement, we measured oxygen saturation in the brain.

Material and Methods

To measure changes in the oxygen saturation of regional brain tissue (rctSO2) before, during and after clamping the jugular veins, we applied two sensors in the left and right frontal region, and we connected them to a biosignal recorder (Invos-5100 system).

Results

Closing or opening the IJV produced significant changes in the rctSO2 values. Before clamping, saturations varied between 77% - 78%, while during clamping they decreased reaching values between 48% - 58% (p <0, 05). After declamping, the rctSO2 returned to its starting values. These results confirmed that obstruction of the jugular veins causes a significant reduction in rctSO2 values and cerebral hypoperfusion.

Conclusions

In MS patients, chronic jugular veins stenosis generates two different clinical pictures:

Diffuse cerebral hypoperfusion, documented by the lowering of rctSO2.

Systemic-cerebral shunt and inversion of cerebral venous circulation capable of causing a breakdown of the blood-brain barrier (BBB)

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Introduction

While the relationship between chronic stenosis of the inferior vena cava and hypoxia of the liver tissue are well known, there are few studies on the relationship between chronic stenosis of the superior vena cava system and hypoxia of the brain tissue [1].

In 1991 Gonzalez-Fajardo et al., in an experimental study of 12 hybrid dogs, showed how occlusion of the superior vena cava causes a rapid increase in central venous pressure and central intracranial pressure [2]. In the following years, Plöchl et al. confirmed that occlusion of the superior vena cava causes a reduction in cerebral perfusion pressure. Based on these studies, from May 2011 to April 2019, to improve brain perfusion, we operated on 152 patients with multiple sclerosis (MS) and stenosis of the internal jugular veins [3]. As reported in previous studies, surgery has shown that there is a constant association between multiple sclerosis and venous stenosis and that vascular obstruction was localised primarily at the junction between the brachiocephalic vein and the jugular vein [4, 5].

The preoperative angiographic analysis confirmed that reversal of cerebral venous blood flow occurred in all patients. At the same time, the use of NIRS revealed how an obstacle to the outflow of blood from the cerebral circulation caused the same stagnant hypoxia caused by a drop-in blood pressure or low cardiac output. Recent perfusion-weighted imaging studies have shown that two clinical pictures characterize multiple sclerosis: diffuse progressive axonal degeneration and focal and intermittent inflammatory demyelination [6, 7].

We hypothesized that the two clinical pictures are due to stenosis of the jugular veins [8-11]. This work aims to demonstrate how jugular vein stenosis is capable of causing cerebral hypoperfusion. The mechanisms by which inversion of cerebral venous circulation can lead to a laceration of the BBB and the formation of new plaques will also be discussed.

Materials and Methods

From February to Joule 2019, 35 patients with chronic stenosis of the internal jugular veins and suffering from multiple sclerosis underwent surgical enlargement of the jugular veins through a patch in the saphenous vein or bovine pericardium. During surgery, we measured brain oxygen saturation in the tissues (rctSO2) using an INVOS system before (T0), during (T1) and after blocking [12].

We have created a local database with various sections completed consecutively by the cardiac surgeons, involved in the care of the patients.

Twenty patients were female, and the mean age was 46 ± 8 years. Median Systemic Arterial Pressure (MAP), Central Venous Pressure (PVC), Jugular Venous Pressure (PVG) and rctSO2 were measured before (T0), during (T1) and after (T2) the internal jugular vein clamping.

Statistical Analysis

The purpose of the analysis is to evaluate for each patient significant changes in the parameters considered between instants T0, T1 and T2. The data set was made up of 35 cases; therefore, we used the associated Student t-test (13) commonly used in such situations: for each parameter, the average of the differences between the values observed in two instances by the patients is considered [13]. In fact, the null hypothesis was "the average of the differences between the values observed in two instants is zero" [14]. Furthermore, since in our analysis the value measured in an instant was expected to be higher or lower than the value measured in a previous instant, Student's t-test with a tail was considered For this test, since the hypothesis nothing has not occurred, we can conclude that the value measured in a time instant is lower or higher than the value measured in a different time instant, depending on the case [15].

Result

During surgery, the mean blood pressure (MAP) was 76 ± 4 mmHg, and the mean venous pressure in the central vein (CVP) and the jugular vein was 6 ± 2 mmHg. The mean systemic oxygen saturation was 95±2%. After clamping, while the PVC remained unchanged, the pressure in the jugular vein (JVP) increased and reached values between 16 and 30mmHg (mv 22 mmHg).

Before clamping the jugular veins, the rctSO2 values varied from 77% to 82%; (mv 78%); during clamping, its value started to decrease until reaching the value of 46 - 58% (mv 55%). After the declamping, the rctSO2 value has progressively increased again until reaching values of 75-79% (mv77%). \

In all patients, there was a decrease in rctSO2 greater than 20 mmHg. These results demonstrate, for the first time, that blockage of the jugular veins leads to a significant increase in pressure in the jugular veins and a constant reduction of rctS02.

Discussion

Multiple sclerosis is considered an autoimmune disease characterized by multifocal areas of inflammation and demyelination within the central nervous system. Even today, although the loss of integrity of the BBB is its hallmark, the mechanism that triggers the disease remains elusive.

Recent perfusion-weighted imaging studies have instead shown that multiple sclerosis is characterized by two distinct clinical pictures: focal and intermittent inflammatory demyelination and widespread progressive axonal degeneration.
The inflammatory process remains localized, episodic, and with a limited duration in time [16].

The degenerative picture, documented histopathologically by Henderson and Prineas, has an independent clinical course, is widespread throughout the brain tissue and remains for the duration of the disease [17]. It is due to cerebral hypoperfusion and has an unknown etiopathogenesis.

The constant association between MS and jugular vein stenosis reported in all 152 operated patients and the constant and significant lowering of rctSO2, obtained in all 35 patients studied with NIRS, suggests that jugular vein stenosis can cause both cerebral hypoperfusion and rupture of the BBB.

Relationship between Jugular Venous Stenosis and Cerebral Hypoperfusion

In recent years, with the introduction of NIRS in cardiac surgery, it has been possible to describe a direct relationship between venous obstruction and cerebral hypoperfusion.
In 2004, using NIRS during an extracorporeal circulation operation, found a decrease in brain oxygen saturation even in the presence of normal blood pressure and normal systemic oxygen saturation [18]. The subsequent correction of wrong positioning of the venous cannula in the superior vena cava led to a normalization of oxygen saturation. The authors speculated that the cause of cerebral hypoperfusion could be related to obstruction of the superior vena cava. To support this hypothesis, they conducted an experimental study on 15 piglets and showed that occlusion of the superior vena cava causes the same reduction in brain oxygen saturation caused by arterial hypotension. Other experimental studies subsequently confirmed these results. Rodriguez, associating NIRS with electroencephalography, documented that transient obstruction of the superior vena cava caused an increase in central venous pressure, a decrease in rctSO2 and a modification of EEG [19].

In 2010, used NIRS, showed that stenosis of more than 75% of the lumen caused a significant reduction in rctSO2 in 18 pigs [20].

This data highlights the concept that the obstruction to the outflow of the cerebral venous circulation causes the same stagnant hypoxia due to low cardiac output or arterial hypotension By monitoring brain perfusion during jugular vein blockage, we have confirmed that closure of the jugular vein causes a significant lowering of rctSO2 and cerebral hypoperfusion.

Furthermore, separate monitoring of central venous pressure (PVC) from that of the jugular vein has shown that, during the lowering of rctSO2, there is only an increase in the values in the jugular vein. While MAP, PVC and systemic oxygen saturation are unchanged. This behaviour indicates that it is a jugular venous obstruction that causes cerebral hypoperfusion and not a low cardiac output or a decrease in AP.

b) Relationship between Jugular Venous Stenosis and BBB Rupture with Plaque Formation

Since the time of Charcot numerous anatomopathological and experimental studies have considered venous circulation as a fundamental factor in the formation of inflammatory plaques in MS [21]. However, the force capable of causing a disruption of the BBB remained unknown.

We hypothesized that three factors mainly contribute to determining plaque formation:
1) Inversion of cerebrospinal circulation
2) Thoracic pump and
3) Embryological isolation of diencephalic tissue.

1) Reversal of Cerebrospinal Circulation

Batson's studies have shown that cerebrospinal venous circulation has no valves, has bidirectional flow and functions as a single conduit connecting the superior vena cava with the inferior vena cava [22].

Based on these studies, it has been demonstrated angiographically that in the presence of a stenosis of the jugular veins there is an inversion of the cerebral venous circulation and the venous blood coming from the head, mouth and neck must pass through the veins of the brain to reach the heart [4, 5]. Viruses or bacteria present in the oral cavity can directly reach the brain tissue.

The systemic-cerebral shunt and the inversion of the circulation give rise to a new circuit that originates from the jugular vein, crosses the sigmoid sinus and the transverse sinus and directly reaches the straight sinus. It has functional characteristics very similar to those of an arterial circuit and is connected to the thoracic cavity by the superior vena cava.

2) The Thoracic Pump and the Rupture of the BBB.

The inversion of the flows alone is not capable of causing a laceration of the BBB but allows the thoracic pump to directly reach the peripheral venous territories of the straight sinus. It is known that, in the Valsalva maneuvers (VM), different levels of expiratory tension can increase intrathoracic pressure from a few to values greater than 150 mm Hg.

Powerful Valsalva maneuvers can cause hypertensive waves so that they directly reach the peripheral veins of the straight sinus and interrupt the BBB [23]. Intra-parenchymal microhemorrhages and the presence of viruses or bacteria in the bloodstream can trigger an inflammatory process and promote the formation of new plaques.

3) Relationship between Embryology and Anatomical Isolation of the Vascular Circulation of the Diencephalon.

The walls of the diencephalon develop before those of the telencephalon. Anatomical and functional isolation makes the vascular network of the diencephalon exposed to increases in blood pressure. Microhemorrhages occur more frequently in the terminal branches of the diencephalic arteries [24].

In addition, in IJV stenosis, hypertensive venous episodes reach the terminal branches of the straight sinus and more easily cause microhemorrhages. The anatomical isolation of the vascular circulation of the diencephalon also limits the formation of plaques, mainly in its territory. In 2016 with the use of MRI has shown, in patients with MS, a higher number of brains microhemorrhages than in healthy subjects and that their distribution was the highest in the diencephalic region [25].

For the reversal of the flows, many of the diencephalic microhemorrhages can be caused not by arterial hypertension but by high increases in PVC. Plaque formation is caused by the association between microhemorrhages and passage of viruses or bacteria from the bloodstream to the brain tissue.

The confirmation that the stenosis of the caval system causes a laceration of the BBB in the cerebral venous territory comes from experimental studies on rats conducted [26, 27]. Using intravital microscopy, the authors showed that, by closing the superior vena cava, an interruption of the BBB was provoked. With the injection of fluorescein-labelled dextran, it was revealed that the leakage of contrast was always localised in the venules of the diencephalic tissue.

Hundreds of scientific articles, based on autopsy studies, have documented how the vein has always been at the centre of the lesion. Recent studies conducted with 3T and 7T magnetic resonance in patients with MS have allowed the visualization of the association between inflammatory plaque and perivenular lesions. These lesions were called "central vein sign" and used as a marker for the diagnosis of multiple sclerosis with magnetic resonance imaging. All these data suggest that the breakdown of the BBB is due to rapid and violent increases in PVC and that microhemorrhages are always perivenular [28]. The passage from the bloodstream into the brain tissue of viruses, macrophage, bacteria, activate all those processes, well described in the literature, which cause the attack and destruction of myelin.

Conclusion

It is possible to state that jugular vein stenosis is the cause of multiple sclerosis. It works using two different mechanisms: stagnant hypoxia and the reversal of flows in the cerebral venous circulation. Cerebral hypoperfusion, resulting from stagnant hypoxia, originates with the onset of multiple sclerosis, is widespread throughout the brain, remains for the duration of the disease and is the main cause of the de-

struction of brain tissue. The rupture of the BBB and plaque formation is episodic, are present only in the RR phase and mainly affects the diencephalic tissue. It is possible to hypothesise that stenoses of the arterial system and stenoses of the venous system may be the basis of all neurodegenerative diseases. We believe that the use of MRI and NIRS and other diagnostic aids will make it possible to clarify whether and how arteriovenous stenosis can lead to the destruction of brain tissue especially in patients with Alzheimer's disease.

Abbreviations

(BJVJ): Brachiocephalic Jugular Veins Junction; (NIRS): near-infrared spectroscopy; (BBB): blood-brain barrier; (rctSO2): Regional Cerebral Tissue Oxygen Saturation; PVC: central venous pressure; MS: multiple sclerosis; (MRI): magnetic resonance imaging; SVC: superior vena cava; (MAP): Median Arterial Pressure; (PVG): Jugular Venous Pressure; (PTA): percutaneous transluminal angioplasty.

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