Effects of Bilateral Jugular Vein Ligation on the Structure and Histochemistry of the Brain in Albino Rat

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Introduction

A hypothesis linking multiple sclerosis to a series of cerebrospinal venous malformations was suggested, the disease entity was named “chronic cerebrospinal venous insufficiency” (Zamboni *et al*., 2009a).

Chronic cerebrospinal venous insufficiency (CCSVI) comprises a series of stenotic malformations affecting the extracranial cerebrospinal venous outflow routes mainly the internal jugular and azygous veins (Ghezzi *et al*., 2010).

The chronic insufficient venous drainage occurring in the course of CCSVI was postulated to cause MS (multiple sclerosis) through the deposition of iron in the walls of the congested veins and in the brain tissue (Zivadinov *et al*., 2010).

Iron overload is assumed to act as a causal factor in the development of MS lesions either directly via oxidative stress or indirectly by acting as a potent

chemotactic factor attracting macrophages and causing the primary activation of the autoimmune cascade (Porto and De Sousa, 2007). Abnormal iron accumulation in the brain substance has previously been associated with aging and with neurodegenerative diseases particularly Parkinson's and Alzheimer's diseases (Stankiewicz *et al.*, 2007 and Stankiewicz and Brass, 2009).

Other studies propose that iron deposition in MS may be secondary to chronic inflammation, iron deposits may be derived from myelin and oligodendrocyte debris, destroyed macrophages, or hemorrhages from damaged brain vessels (Singh and Zamboni, 2009).

The initial studies on CCSVI exhibited a near 100% specificity and sensitivity to MS (Embry, 2010), however subsequent studies showed conflicting results and have not been able to prove a definitive

confirmation of the proposed hypothesis (Sundstrom *et al*., 2010).

As a consequence of the new hypothesis, Percutaneous transluminal angioplasty and stenting were applied as potential treatment alternatives for MS patients (Zamboni *et al*., 2009b), on the other hand the procedure is invasive and has shown serious side effects including stent migration, cerebral hemorrhage, jugular vein thrombosis, and even death (Samson, 2010).

Given the fact that hitherto no definite cure is known for MS (Linker *et al*., 2008) and the hope that this new hypothesis might give to about two million patients worldwide, and also considering the risk of the new treatment modality; It is therefore indispensable that further studies be carried out to verify the role of the venous malformations on the development of MS and the role of iron in its pathogenesis.

To date, a limited trial has been attempted to create an animal model of CCSVI, bilateral jugular venous ligation was performed and the mice models were evaluated for inflammation and demylination, however detection of iron in rat model of CCSVI was never attempted (Atkinson *et al*., 2012).

Given the insufficient evidence and the conflicting data concerning the role of CCSVI in the etiology of MS and the source of iron in the course of MS, the present study aims to investigate this hypothesis in a controlled animal model by creating CCSVI in rat.

Aim of Work

The aim of this work was to study the effect of bilateral jugular venous ligation on rat brain and to assess its effect on:

1. Integrity of the nervous system by standardized neurological assessment.
2. Histology of white matter.
3. Iron deposition.
4. Integrity of myelin in various areas.
5. Histochemistry of astrocytes, microglia and lymphocytes.
6. Image and Statistical analysis for the number of myelinated fibers in semithin sections, the area percentage of iron deposition and myelin content, the area percentage of immunoreactivity to glial fibrillary acidic protein, CD68 and CD45 and the number and the size of astrocytes.

Multiple Sclerosis: Pathogenesis and Proposed Etiologies

MS is a chronic, debilitating, incurable demyelinating disease of the central nervous system, affecting up to 2.5 million people worldwide and is one of the leading causes of disability in young adults (Ganesh and Stahnisch, 2013).

Regarding its pathology, MS is described as an acute focal inflammatory demyelination that leads to slowing or loss of impulse transmission (Reipert, 2004).

The lost myelin is eventually replaced by an astrocytic scar with the development of the pathological hallmark of chronic MS: the demyelinated plaque (Noseworthy *et al*., 2000), once the axons have become scarified they never fully regain their former function (Reipert, 2004).