

# Acetazolamide as a medical treatment option for patients with neurodegenerative disease in conjunction with or independent of, angioplasty for Chronic Cerebrospinal Venous Insufficiency (CCSVI)

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## Introduction

With the advent of research involving chronic cerebrospinal venous insufficiency (CCSVI) in patients with neurodegenerative disease, new explanations for decreased oxygen perfusion of the brain and the potential for Idiopathic Intracranial Hypertension need to be considered.

Recent studies using perfusion magnetic resonance imaging in both relapsing and progressive forms of MS have shown decreased perfusion of the Normal Appearing White Matter (NAWM), which does not appear to be secondary to axonal loss.

Recently, a pilot study indicated that hypoperfusion of brain parenchyma is associated with the severity of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis.

## Purpose

The authors hypothesize that the use of acetazolamide, a carbonic anhydrase inhibitor, to decrease intracranial pressure may offer these patients the benefits of increased cerebral perfusion pressure -- immediate reduction of symptoms of poor oxygen perfusion of the brain.

The first action of acetazolamide is to decrease the production of cerebral spinal fluid.

A second action of acetazolamide is its ability to increase blood flow in the brain. Pickkers et al discuss this in the British Journal of Pharmacology where they conclude that acetazolamide exerts a direct vasodilator effect in vivo in humans mediated by vascular calcium activated potassium channels.

Zaitsu Y and Haacke EM (see references) measured a +39.7% increase in cerebral blood flow using acetazolamide.

## References

- Juurink BH. The multiple sclerosis lesion: initiated by a localized hypoperfusion in a central nervous system where mechanisms allowing leukocyte infiltration are readily upregulated? Med Hypotheses. 1998. Oct;51(4):299-303. PMID: 9824835
- Pickkers P, Hughes A, Russel F, Thien T, Smits P. In vivo evidence for K(Ca) channel opening properties of acetazolamide in the human vasculature. Br J Pharmacol. 2001 January;132(2):443-450.
- Kapadia S, Dibbs Z, Zaitsu Y, Kudo K, Terae S, Haacke EM, et al. Mapping of Cerebral Oxygen Extraction Fraction Changes with Susceptibility-weighted Phase Imaging. Radiology. 2011 Oct. PMID: 22031711
- Newman, NJ; Selzer, KA, Bell RA. Association of multiple sclerosis and intracranial hypertension. Journal of Neuro-Ophthalmology. 14(4): 189 – 192, 1994.
- O'Brien T, Paine M, Matotek K, Byrne E. Apparent hydrocephalus and chronic multiple sclerosis: a report of two cases. Clin Exp Neurol. 1993;30:137-43. PMID: 7712624
- Williams BJ, Skinner HJ, Maria BL. Increased intracranial pressure in a case of pediatric multiple sclerosis. J Child Neurol. 2008 Jun;23(6):699-702. PMID: 18539995
- Walters F. Intracranial pressure and cerebral blood flow. Update in Anesthesia. 1998; Issue 8: Article 4:1-4.
- Zaitsu Y, Kudo K, Haacke EM, et al. Mapping of Cerebral Oxygen Extraction Fraction Changes with Susceptibility-Weighted Phase Imaging. Radiology. 2011 Oct 26. PMID: 2203177

## Methods

This article describes the results of a pilot study of 25 patients with either multiple sclerosis (n=23) or chronic Lyme (n=2) who were prescribed acetazolamide and then evaluated subjectively for a change in symptoms related to poor cerebral perfusion.

### Symptoms evaluated included

- poor sleep and sleep patterns,
- cognitive difficulties (short-term memory issues, loss of executive function, loss of focus),
- change in head discomfort (the "feeling of pressure") or frank headache, and
- fatigue.

**Dosages of acetazolamide** varied, depending on patient age and weight, orthostatic tolerance, reported sensitivity levels to medication and patient response to initial doses.

## Conclusion

**With its multiple mechanisms to increase oxygen perfusion in the brain and other organs of the body, acetazolamide needs to be considered as an adjunctive therapy for diseases resulting in poor oxygen perfusion of the brain.**

The authors encourage double-blind, controlled studies for multiple sclerosis patients, and affected patients of related conditions resulting in poor oxygen perfusion. These conditions may include, but are not limited to: postural orthostatic tachycardia syndrome, chronic fatigue, Parkinson's, Alzheimer's Disease, Devic's Disease, Idiopathic Intracranial Hypertension and small vessel dementia. This list is by no means conclusive and the authors look forward to the possibility that a well known, inexpensive drug (acetazolamide) could provide great relief for these patients, in conjunction with, or independent of angioplasty for CCSVI.

## Results

21 out of 25 patients with chronic Lyme (n=1) or multiple sclerosis (n=20) reported significantly positive changes in:

- sleep (quality and quantity),
- head discomfort (the "feeling of pressure" in their heads) or frank headache
- cognition (short-term memory functions, executive functions and the ability to focus),
- fatigue

**Note:** improvement of sleep and head discomfort occurred overnight. Improvement in cognition and fatigue occurred over weeks to months.

### Side effects included:

- drowsiness
- paresthesias
- worsening of orthostatic tolerance
- dehydration (causing one patient to drop out of the study)

These effects are recognized side effects of acetazolamide and resolved spontaneously or with alterations of dosage or dosing frequency.

## Discussion

Recent studies using perfusion magnetic resonance imaging in both relapsing and progressive forms of MS have shown decreased perfusion of the Normal Appearing White Matter (NAWM), which does not appear to be secondary to axonal loss.

Recently, a pilot study indicated that hypoperfusion of brain parenchyma is associated with the severity of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis.

The authors hypothesize that the use of acetazolamide in these patients assists in brain perfusion through a minimum of two modes of actions:

### 1) CPP = MAP – ICP

Cerebral perfusion pressure equals the mean arterial pressure minus the intracranial pressure. The authors hypothesize that use of acetazolamide, a carbonic anhydrase inhibitor, to decrease intracranial pressure may offer these patients the benefits of increased cerebral perfusion pressure, and the immediate reduction of symptoms of poor oxygen perfusion of the brain.

### 2) A second action of acetazolamide is its ability to increase blood flow in the brain.

Pickkers et al discuss this in the British Journal of Pharmacology where they conclude that acetazolamide exerts a direct vasodilator effect in vivo in humans mediated by vascular calcium activated potassium channels.

In the Pickkers study, acetazolamide infusions increased forearm blood flow, with no significant changes in the non-infused forearm, blood pressure or heart rate.

They conclude that acetazolamide exerts a direct vasodilator effect in vivo in humans mediated by vascular K(Ca) channel activation. They went on to conclude that this makes acetazolamide the first drug known that specifically modulates this channel.

In a study using susceptibility-weighted phase imaging, researchers noted an increase in cerebral blood flow of +39.7% with the use of acetazolamide.