

## NEUROSYPHILIS - THE WHITE MATTER DISINTEGRATION? - TWO CASE REPORTS

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### SUMMARY

**Background:** There is evidence for neurosyphilis being associated with the central nervous system vasculitis involving medium and small vessels. As the hemispheric white matter is the major target of these vascular alterations the white matter axonal and myelination disruption may be observed employing measure for the rate of water molecule diffusion. High apparent diffusion coefficient (ADC) correspond to unimpeded water diffusion and indicating white matter disintegration.

**Case reports:** In a retrospective study exploring central nervous system magnetic resonance (MR) images of two subjects presenting with neurosyphilis the ADC values were found to be increased as related to normal values being accompanied with normal appearing white matter of hemispheres

**Conclusions:** Applying ADC analysis to evaluate the brain in patients with neurosyphilis may reveal undetectable changes and explain the scale of abnormalities that occur in CNS. The increased mean ADC values in the normal appearing white matter of the hemispheres may correlate with neuropsychiatric symptomatology in syphilis.

**Key words:** DWI - neurosyphilis - neuroimaging

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### INTRODUCTION

Syphilis is a sexually transmitted disease caused by *Treponema pallidum*. The invasion of the central nervous system may occur at any stage of the disease and is observed in 5-10% of untreated patients. The diagnosis of the early stage of syphilitic infection is complex as many patients present either nonspecific symptoms or remain asymptomatic (Rozwens 2003, Cubała 2008).

Syphilis and tuberculosis have re-emerged as prominent causes of central nervous system (CNS) vasculitis with the onset of the HIV epidemic (Rozwens 2003). Vasculitis associated with infection can affect vessels of three sizes. In neurosyphilis usually medium and small vessels are involved. The most frequently involved arteries are the middle cerebral artery and branches of the basilar artery (Czarnowska- Cubała., 2013). Vascular pathology as an inflammatory process leads to endothelial damage, blood-brain-barrier breakdown, activation of innate immunity and disruption of trophic coupling between vascular and brain cells. The hemispheric white matter, which is particularly susceptible to the deleterious effects of vascular risk factors, is a major target of these vascular alterations. The resulting demyelination and axonal loss plays a role in the broad functional brain changes underlying cognitive impairment and in the associated cerebral atrophy. This chain of events highlights the critical role that vascular cells play in the maintenance of the health of neurons, glia and myelin (Ladecola 2013).

The diagnosis of CNS vasculitis continues to be a clinical and radiographic challenge. It has been demon-

strated that magnetic resonance (MR) imaging findings in CNS vasculitis can be negative (Calabrese 1997, Denays 1999, Conde-Sendin 2004, Cubała 2008) even in cases of pathologically proven vasculitis (Kararizou 2006). This demonstrates the need for a non-invasive test that can detect abnormalities that may be missed. This test could potentially be beneficial for both diagnostic and prognostic purposes. Diffusion-weighted imaging (DWI) uses a contrast mechanism - water diffusivity - that is unique and quantifiable and allows DWI to demonstrate brain changes that routine MR imaging misses (Conde-Sendin 2004). The degree of white matter axonal and myelination disruption is measured through the rate of water molecule diffusion. High apparent diffusion coefficient (ADC) measures correspond to relatively unimpeded water diffusion, while low ADC measures reflect preserved myelinated axons. In normal white matter, the axons are myelinated and tightly packed in a highly organised extracellular matrix which is largely made up of glial cells and processes. Damage to the axonal membrane, changes in its permeability, reduced integrity of intra-axonal microtubules and axonal de- or dysmyelination have all been suggested to account for pathological increases in ADCs (Beaulieu 1994, Helenius 2002, Giedd 2004). The increased ADC values for normal appearing brain have been found in multiple sclerosis, tuberous sclerosis, Behcet disease, NF1, and the aging brain (Holland et al. 1986, Hunder 1990, Harris 1994, Herald 1996, Gomes 2010). Applying ADC analysis to evaluate the brain in patients with inflammatory vasculitis in neurosyphilis may reveal otherwise undetectable changes.

This study explored cortical white matter microstructure by identified regions of interest (ROIs) distributed over the frontal, temporal, parietal and occipital lobes in a patient with neurosyphilis in order to identify widespread disruption of normal appearing white matter organisation using DWI method.

## METHOD

Retrospectively review of the brain MRIs of two patients with neurosyphilis diagnosis presenting neuropsychiatric symptomatology was performed.

The examination was completed with 3T MR imaging (Philips) by using an 8-channel sensitivity-encoding head coil. DWI, FLAIR, T2-weighted, gradient-echo T2-weighted, T1-weighted and postcontrast T1-weighted Images were obtained. Diffusion-weighted imaging was performed with a spin-echo echo-planar imaging sequence in the axial plane with a TR/TE of 7100/92, a gradient strength of 33mT/m, 45mT/m4-mm-thick sections, an intersection gap of 0.8mm, a field of view of 241/241 mm<sup>2</sup>, and a matrix size of 192/192. Diffusion was measured in three orthogonal directions (x, y, and z) with three b values (0.500 and 1000 s/mm<sup>2</sup>).

The images were displayed on a commercial Philips workstation for the post-processing analyses. Circular ROIs corresponding to an area of 0.18 cm<sup>2</sup> were placed, bilaterally, in the frontal, temporal, parietal, and occipital white matter of hemispheres on the diffusion weighted (b=1000) echoplanar images. The ROIs were automatically transferred to the corresponding maps to obtain the ADC of water molecules. The DW images were correlated with FLAIR images to confirm the normal-appearing white matter. All data were measured independent by the board certified radiologist.

## CASE 1

A 49-year-old Caucasian male with no prior psychiatric history developed cognitive decline accompanied by dysphoria. Being a qualified active baker's confectioner he had lost professional abilities to perform his regular duties associated with complex food preparation processes. Although his co-workers noticed those problems he had not been aware of the decline and argued in a dysphoric manner when the mistakes at work had been addressed. Having been referred to the occupational medicine physician and psychiatrist cognitive deficits had been found.

Blood serum analysis was negative for HIV and *Borrelia*. Syphilis on Wassermann reaction (WR) serum testing was positive being subsequently confirmed with microhemagglutination (MHA-TP) assay. The cerebrospinal fluid analysis as noted for pleocytosis (25/μl) and increased global protein count in cerebrospinal fluid (0.66 G/l) with a positive VDRL test and positive FTA - Abs treponemal antibody absorption test. The patient

reported a year-long history of sight loss. Ophthalmologist consultation revealed possible right eye optic nerve neuropathy with hypertensive angiopathy (2nd degree in both eyes), being probably linked to neurosyphilis.

## CASE 2

A 65-year-old Caucasian woman was admitted on to the psychiatric unit with cognitive impairment. The patient had been treated due to motor disorder accompanied by accumulating cognitive decline observed by her husband for three years and treated in outpatient setting for a year. On admission she presented moderate dementia with generalized cognitive deficits. An in-depth elaboration of her cognitive impairment revealed dysfunction of the visual spatial memory, executive functions, operational memory, verbal memory, learning and attention processes and perception.

On neurological examination symptoms of corticobasal degeneration were observed. She was conscious, verbally responsive, however, with elements of speech disorders characterized by anomia and elements of speech apraxia. The patient presented severe bruxism. Rigidity, bradykinesia and limb apraxia were present being most severely expressed in the upper left limb. On examination involuntary dystonic phenomena occurred with her left arm involuntarily drifting gradually upwards.

Standard laboratory tests were normal. Blood serum analysis was negative for HIV and *Borrelia*. However, syphilis on Wassermann reaction (WR) serum testing was positive being subsequently confirmed with microhemagglutination (MHA-TP) assay. A lumbar puncture was performed and cerebrospinal fluid analysis was noted for protein level of 0.58 g/l, glucose level of 71 mg/l, normal cell count and differential, and a negative VDRL test and positive FTA - Abs treponemal antibody absorption test.

## RESULTS

In both studied cases the increase of ADC value throughout the normal appearing white matter of hemispheres was detected (Table 1). There is little data on the normal ADC values in the white matter of the brain. Helenius et al. (2002) in a group of 80 subjects determined that the mean ADC values in the white matter were  $0.70 \pm 0.03 \times 10^{-3} \text{ mm}^2/\text{sec}$  (range  $0.62 - 0.79 \times 10^{-3}$ ). No significant changes were observed between the age, sex and hemispheres. We used the data as a references.

In Case 1 the changes of ADC value were detected only in the left temporal lobe. In Case 2 the ADC values changes were more intense and were detected in both occipital and temporal lobes and also in left frontal and right parietal lobe.

**Table 1.** ADC values throughout the normal appearing white matter of hemispheres

Lobe	Case 1		Case 2	
	Mean ( $10^{-3}/\text{mm}^2/\text{sec}$ )	Area $0.18\text{cm}^2$	Mean ( $10^{-3}/\text{mm}^2/\text{sec}$ )	Area $0.18\text{cm}^2$
Frontal R		0.713		0.751
Frontal L		0.777		0.832
Occipital R		0.725		0.924
Occipital L		0.683		0.809
Parietal R		0.729		0.842
Parietal L		0.748		0.752
Temporal R		0.648		0.841
Temporal L		0.869		0.910

## DISCUSSION

The study detected the increase of the ADCs throughout the white matter of almost all brain lobes. The differences in the intensity of ADC value were noticeable between the subjects observed with increased ADC values noted in the case of cortical atrophy being probably also associated with brain ischemic changes.

The results of study corroborate with diffuse changes observed in the normal-appearing brain in patients with CNS vasculitis where the ADCs were increased throughout the white matter of the corona radiata and centrum semiovale, the thalami, and the posterior internal capsules (White et al. 2007).

This study demonstrated the ability of ADC measurements to detect brain changes that have not been previously noted. It may be hypothesized the ADC analysis may be indicative of the diffuse abnormalities detected and potentially represent diffuse vasogenic edema, brain destruction (axonal loss), Wallerian degeneration, or vascular changes directly due to the vasculitic process along with age associated processes, i.e. ischemic changes. In patients with CNS vasculitis, diffuse pathologic changes in the brain parenchyma include loss of nerve cells, abnormal nerve cells, perivascular lakes of eosinophilic material, and foci of vacuolation (Küker 2007). On autopsy, the diffuse edema, reactive astrocytosis, ischemic change, and hemorrhage have been identified (White 2007).

There is no specific normative value for ADC of white matter. Studies on absolute ADC values in the normal human brain are scarce and only a few reports have been published. Applying ADC analysis to evaluate the brain in patients with neurosyphilis may reveal undetectable changes and explain the scale of abnormalities that occur in CNS (White 2007). Further analysis of patients with neurosyphilis is needed to determine if this information can be used to predict patient diagnosis, acute clinical outcome, or long-term disability.

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**Conflict of interest:** None to declare.

### Contribution of individual authors:

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