HEREDITARY DIFFUSE LEUKOENCEPHALOPATHY WITH SPHEROIDS
INSIGHTS INTO AN ADULT ONSET NEURODEGENERATIVE DISEASE

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The thesis is based on the following papers

I. Update of the original HDLS kindred: divergent clinical courses.


II. Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS): a misdiagnosed disease entity.


III. Mutations in the colony stimulating factor 1 receptor (CSF1R) gene cause hereditary diffuse leukoencephalopathy with spheroids.


IV. MRI characteristics and scoring in HDLS due to CSF1R gene mutations.


V. Different stages of white matter changes in the original HDLS family revealed by advanced MRI techniques.

Sundal Christina, Jönsson Lars, Ljungberg Maria, Zhong Jianhui, Tian Wei, Zhu Tong, Linden Thomas, Börjesson-Hanson Anne, Andersen Oluf, Ekholm Sven.
Journal of Neuroimaging. Accepted for publication 2013, ID JON-13-3632.R1.

During the last three decades, the areas of inherited white matter (WM) disorders have expanded. Advances in magnetic resonance imaging (MRI) and genetics have led to increased detection of adult-onset WM disorders. Hereditary diffuse leukoencephalopathy with spheroids (HDLS) is an adult-onset, invariably lethal, brain WM disorder with an autosomal dominant inheritance pattern. The clinical symptoms are characterized by a constellation of features that progress to a devastating disease with multiple neurological impairments. The neuropathological hallmarks of HDLS are demyelination and the presence of axonal spheroids.

The overall aim of this study was to gather enough clinical cases, radiological images, cerebrospinal fluid (CSF) biomarkers and molecular genetic data to place HDLS in a nosographic context and define its relationship with other neurodegenerative disorders.

We updated the original Swedish HDLS family and created a pedigree consisting of 166 individuals. Fifteen of those cases were affected with HDLS, including two new cases. The clinical course was different in the two recent cases, with a sub-acute and a more chronic variant, respectively. Familial clustering of HDLS is not always obvious and in the Mayo Clinic HDLS collection we found that all of our cases had been misdiagnosed with other more common neurological disorders. Using exome sequencing, we identified the colony stimulating factor 1 receptor ($\text{CSF1R}$) mutation in 14 Mayo Clinic HDLS families. MRIs of 15 of these $\text{CSF1R}$ mutation carriers demonstrated asymmetric WM lesions (WML) with frontoparietal predominance. With diffusion weighted-, and diffusion tensor imaging (DTI/DWI) we defined three different stages of HDLS pathology, and detected a peripheral rim of restricted diffusion that had a centrifugal migration from the anterior ventricular horns. This might be pathognomonic for the original Swedish type of HDLS.

In conclusion, HDLS is a distinct disease entity and the combination of clinical features such as frontal lobe syndromes, pyramidal-, extrapyramidal-, parietal- and visual signs, as well as WML in a characteristic frontoparietal distribution gives diagnostic clues. To clarify the distinction between the unknown genetics of the original Swedish family and the $\text{CSF1R}$ mutation carriers, we propose to use molecular classification of HDLS type 1 and type 2, respectively. Results from our studies indicate that HDLS is probably primarily a neuroaxonal degeneration. Thus, elucidating the molecular mechanism of HDLS may provide novel insights into neurodegeneration.