Pathological progression of multiple sclerosis documented—possible new treatment options

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The Centre for Brain Research at the MedUni Vienna is regarded as a world leader in researching the mechanisms involved with multiple sclerosis (MS). Now, in a paper published in the highly respected journal *Lancet Neurology*, an international team of researchers from Edinburgh, Cleveland and Vienna, under the leadership of Hans Lassmann, Head of the Department of Neuroimmunology at the MedUni Vienna, has for the first time documented the pathological progress of the disease from its early to late stage and also shown that inflammatory and neurodegenerative processes have a role to play. This raises the possibility of new treatment options.

Until now, there have been two approaches to categorising the condition: the first approach regards MS as a disease of the nervous system that is inflammatory throughout, with the inflammation also being responsible for the subsequent neurodegenerative damage. The second approach postulates that the disease ultimately progresses from an inflammatory condition into a neurodegenerative one. In their current paper however, the team of researchers has demonstrated that multiple sclerosis is comprised of both factors - and that the inflammatory process acts as a "driving force" from the onset right to the end, and that neurodegenerative processes also occur in the so-called progressive, late phase that damage the brain.

Says Lassmann: "The inflammatory process, which can be treated effectively in the early stages, becomes less pronounced with age. However the neurodegenerative damage increases. This also explains

why drugs that initially work well later lose their effectiveness."

In the later stages of the condition, "amplification mechanisms" are triggered: the damage becomes amplified - and in a "self-contained" cycle that continues to cause destruction. The neurodegenerative damage in the brain activates microglial cells that also drive the disease forward, along with the formation of oxygen radicals that destroy lipids and proteins in the brain. At the same time, damage occurs to the mitochondria, which act as the power plants and energy providers to cells in the brain. This - coupled with normal brain ageing and the associated deposition of iron - also causes further damage.

New approaches to treatment could be developed based on the new discoveries about all of these mechanisms, say the researchers. "There are two routes", says Lassmann. "First, drugs could be developed that have an anti-inflammatory effect in the brain too, not just suppressing the defence response in the blood and lymphatic organs. Secondly, neuroprotective treatments could be developed that preventively block the amplification mechanisms and damage to the mitochondria, thereby preventing consequential damage."

Clinical studies involving a number of potentially useful medications are already under way on the basis of this new data. The results will not be known for at least five years, however, explains Lassmann: "I firmly believe that in the foreseeable future, so within the next five to ten years, we will be successful in fighting the amplification mechanisms and slowing down the progressive phase further."

This amplification cycle in the brain is also seen in other neurodegenerative conditions such as Alzheimer's or Parkinson's disease, but also as part of the brain's normal ageing process. As a result, the new treatments from MS research could be useful for these conditions, too.

2.5 million people worldwide affected

Around 8,000 Austrians are affected by multiple sclerosis. The condition affects around 2.5 million people worldwide. MS is a chronic inflammatory disease of the central nervous system in which the insulating layers of the nerve fibres are destroyed. The mechanisms of the inflammatory process in the nervous system are largely understood. This knowledge has given rise to effective treatments that can delay the disease's progression. In people with advanced stages of the disease, however, these treatments appear to only have a very limited effect. The exact cause of MS is so far not fully understood. It is possible that an autoimmune cause is the culprit. Equally, the excessive immune response may be acting against an infectious pathogen that has not yet been identified.

More information: "Pathological mechanisms in progressive multiple sclerosis." *The Lancet Neurology* , Volume 14, Issue 2 , 183 - 193 DOI: dx.doi.org/10.1016/S1474-4422(14)70256-X

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