The brake on neurodegeneration
Increased mitochondrial metabolism in the injured MS spinal cord

In this issue of Neurology®, Ciccarelli et al.¹ present an intriguing study assessing 14 patients with multiple sclerosis (MS) at the time of an acute relapse related to a lesion at the spinal C1–C3 level. The authors performed magnetic resonance spectroscopy (MRS) and atrophy measurements on spinal cords of these 14 patients with MS and 13 age- and gender-matched healthy controls. Spinal N-acetylaspartate (NAA) concentrations were calculated at baseline and followed for 1, 3, and 6 months, as was spinal cord cross-sectional area. The investigators found that after an initial decrease in the first month, NAA levels recovered partially in the months after the inflammatory demyelinating event, and that patients who recovered showed a greater increase in NAA after 1 month. Spinal cord cross-sectional area gradually decreased over time and was independent of NAA recovery and, interestingly, of clinical outcome. The authors report that longer disease duration at baseline predicted less NAA recovery over time, suggesting that repair processes become “burnt-out” (i.e., less effective) with progressing disease.

NAA is abundantly present in the human CNS, especially in neurons, and decreased levels of NAA, as measured with MRS, are therefore used as a marker for neuronal loss or dysfunction. Although the exact function of the metabolite is still debated, it is known that it is synthesized in neuronal mitochondria, and changes in NAA levels thus point to abnormal mitochondrial metabolism, which in turn may lead to neurodegeneration. Ciccarelli et al. point out that the initial decrease in NAA (during the first month of their study) is in line with decreased mitochondrial activity, which is probably related to the interaction of axons with microglia and other immune modulators.² The subsequent NAA increase may reflect increased mitochondrial numbers or activity or both, all in an attempt to maintain axonal electrical conduction. Increased numbers of mitochondria and enhanced activity of mitochondrial complex IV were indeed found in histopathologic studies investigating demyelinated axons in actively demyelinating and chronic MS lesions,²,³ and may be considered as an endogenous protective mechanism of the CNS to repair damage after an inflammatory demyelinating insult.

However, whether increased mitochondrial activity is to be considered beneficial in the long run is a question worth delving into further. Mitochondria are an important source of reactive oxygen species (ROS); hence, it is conceivable that prolonged mitochondrial overactivity might contribute to the formation of highly toxic oxygen radicals and concomitant oxidative tissue injury. Increased ROS production and enhanced expression and activity of nitric oxide synthase inhibits the mitochondrial electron transport chain, which, in turn, leads to increased mitochondrial ROS production, adenosine triphosphate depletion, and disturbed Ca²⁺ homeostasis due to reversed Na⁺/Ca²⁺ transporter activity. Together, these detrimental changes impair mitochondrial function and subsequent energy production, ultimately resulting in axonal death.⁴ We previously showed that mitochondria in MS lesions are subjected to oxidative stress as indicated by enhanced expression of the mitochondrial heat shock protein 70.⁵ In addition, several reports have demonstrated the occurrence of ongoing oxidative damage in MS brain tissue.⁵

The findings by Ciccarelli et al.¹ in combination with the above discussed histopathology studies²,³ emphasize that mitochondrial dysfunction is an important pathologic hallmark in MS and that strategies aimed at improving mitochondrial function may limit disease progression. Previously, NAA recovery in MS was reported to occur after treatment with interferon beta-1b and glatiramer acetate,⁶,⁷ which suggests that currently available medication might already be of use in treating and partially reversing axonal damage related to mitochondrial dysfunction. However, more targeted therapies that boost endogenous levels of mitochondria-specific antioxidant enzymes, such as superoxide dismutase 2,⁸ or administration of antioxidant compounds...
that selectively accumulate in mitochondria, e.g., mito-
quinone (MitoQ), may be even more effective. MitoQ
represents a novel class of powerful antioxidants that,
because of their positive charge, specifically accumulate
within mitochondria. Recently, it has been shown that
MitoQ has therapeutic potential in vivo, because it
blocked mitochondrial oxidative damage and greatly re-
duced tissue damage in a cardiac ischemia-reperfusion
model. Currently, phase 2 trials are ongoing to explore
the efficacy of MitoQ in a human setting. Future explor-
ative clinical trials using mitochondrial antioxidants
could rely on the MRS approach adopted by Ciccarelli
et al. to monitor NAA recovery over time, in relation to
tissue atrophy.

It has been repeatedly demonstrated that in re-
sponse to tissue damage in MS, repair processes oc-
cur throughout the entire CNS. Aside from the
increases in mitochondrial number and function al-
ready discussed, and the redistribution of axonal so-
dium channels in an attempt to maintain axonal
function upon demyelination, remyelination and ex-
tensive use of the reserve capacity of the brain were
found. Unfortunately, however, all these compen-
satory changes are finite, and relentless neurode-
generation will eventually set in. In the study by
Ciccarelli et al., longer disease duration predicted less
NAA recovery, which underlines the limits of compen-
satory changes over time. This might explain why
the rate of gray matter atrophy suddenly starts accel-
erating around the conversion point from relapsing-
remitting to secondary progressive disease: the
brake on neurodegeneration is released.

ACKNOWLEDGMENT
The authors thank Dr. M.E. Witte from the Department of Pathology of
the VU University Medical Center for helpful discussions.

DISCLOSURE
Dr. Geurts serves on the editorial board of MS International and the
Scientific Advisory Board of the Dutch MS Research Foundation. Dr. van
Horssen receives research support from the Dutch Foundation of MS
Research and the Dutch Brain Foundation.

REFERENCES
repair in MS: does mitochondrial metabolism play a role?
changes within axons in multiple sclerosis. Brain 2009;
132:1161–1174.
and activity of mitochondria in multiple sclerosis lesions.
4. Trapp BD, Stys PK. Virtual hypoxia and chronic necrosis
of demyelinated axons in multiple sclerosis. Lancet Neurol
5. van Horssen J, Schreibelt G, Drexhage J, et al. Severe oxi-
dative damage in multiple sclerosis lesions coincides with
enhanced antioxidant enzyme expression. Free Radic Biol
metabolic recovery in multiple sclerosis patients treated
and potential neuroprotective effect of glatiramer acetate
11:646–651.
8. Qi X, Sun L, Lewin AS, Hauswirth WW, Guy J. Long-
term suppression of neurodegeneration in chronic experi-
mental optic neuritis: antioxidant gene therapy. Invest
9. Murphy MP, Smith RA. Targeting antioxidants to mito-
chondria by conjugation to lipophilic cations. Annu Rev
endothelial function and attenuates cardiac hypertrophy.
11. Franklin RJ, Ffrench-Constant C. Remyelination in the
CNS: from biology to therapy. Nat Rev Neurosci 2008;9:
839–855.
changes in patients with multiple sclerosis and nonspecific
findings on conventional magnetic resonance imaging
atrophy in multiple sclerosis: a longitudinal study. Ann
The brake on neurodegeneration: Increased mitochondrial metabolism in the injured MS spinal cord
Jeroen J.G. Geurts and Jack van Horssen

Neurology 2010;74;710-711 Published Online before print January 27, 2010
DOI 10.1212/WNL.0b013e3181d1cd76

This information is current as of January 27, 2010

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: <a href="http://n.neurology.org/content/74/9/710.full">http://n.neurology.org/content/74/9/710.full</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td>This article cites 13 articles, 3 of which you can access for free at: <a href="http://n.neurology.org/content/74/9/710.full#ref-list-1">http://n.neurology.org/content/74/9/710.full#ref-list-1</a></td>
</tr>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s):</td>
</tr>
<tr>
<td></td>
<td>All Spinal Cord <a href="http://n.neurology.org/cgi/collection/all_spinal_cord">http://n.neurology.org/cgi/collection/all_spinal_cord</a></td>
</tr>
<tr>
<td></td>
<td>DWI <a href="http://n.neurology.org/cgi/collection/dwi">http://n.neurology.org/cgi/collection/dwi</a></td>
</tr>
<tr>
<td></td>
<td>MRI <a href="http://n.neurology.org/cgi/collection/mri">http://n.neurology.org/cgi/collection/mri</a></td>
</tr>
<tr>
<td></td>
<td>MRS <a href="http://n.neurology.org/cgi/collection/mrs">http://n.neurology.org/cgi/collection/mrs</a></td>
</tr>
<tr>
<td></td>
<td>Multiple sclerosis <a href="http://n.neurology.org/cgi/collection/multiple_sclerosis">http://n.neurology.org/cgi/collection/multiple_sclerosis</a></td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.neurology.org/about/about_the_journal#permissions">http://www.neurology.org/about/about_the_journal#permissions</a></td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: <a href="http://n.neurology.org/subscribers/advertise">http://n.neurology.org/subscribers/advertise</a></td>
</tr>
</tbody>
</table>

Neurology © is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright . All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.