Insulin-like growth factor system in human central nervous system, multiple sclerosis and amyotrophic lateral sclerosis

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Chapter 6

**Insulin-like growth factor system in serum and cerebrospinal fluid in patients with multiple sclerosis**

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Abstract

The insulin-like growth factor (IGF) system influences oligodendrocyte survival, myelination, and immune functions. We examined whether alterations in the circulating IGF system occur in multiple sclerosis (MS), a chronic inflammatory demyelinating disease of the central nervous system. We measured concentrations of IGF-I, IGF-II, and insulin-like growth factor binding proteins -1, -2, and -3 in both serum and cerebrospinal fluid from MS patients and age- and sex-matched controls. IGFBP-1 was not detectable in cerebrospinal fluid. We found no significant differences in any of the other components between patients with MS and controls.
Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system of unknown cause that affects about 1 per 1000 in high prevalence areas. The pattern of inflammation in MS brains is in agreement with a T-cell mediated inflammatory process and epidemiological studies support both genetic and environmental components of susceptibility. The insulin-like growth factor (IGF) system may be of interest in MS because it has trophic effects on oligodendrocytes, stimulates myelination, and regulates immune mechanisms.

The system consists of two insulin-like growth factor peptides (IGF-I and IGF-II), two IGF receptors, at least seven IGF-binding proteins (IGFBPs), IGFBP cell surface receptor proteins, and IGFBP proteases. IGF-I and IGF-II circulate in blood and cerebrospinal fluid, where they are complexed to IGFBPs. These circulating IGFBPs are responsible for transport of the IGFs to their target tissues. In blood IGFBP-3 is the prominent binding protein, whereas IGFBP-2 is the major form in cerebrospinal fluid.

IGF-I promotes the survival and regeneration of oligodendrocytes in culture systems, and it stimulates the synthesis of myelin by regulating the expression of myelin genes, including myelin basic protein and proteolipid protein. Transgenic mice, which overexpress IGF-I, have an increased myelin content in their central nervous system. IGF-deficient mice that survive show a strong reduction in myelination and the numbers of oligodendrocytes, together with decreased thickness of white matter structures, such as the corpus callosum, anterior commissure, and the fibre bundles in the internal capsule.

Both IGF-I and IGF-II also affect the immune system in several ways. IGF-I increases both the number of T- and B-lymphocytes and stimulates their function, whereas IGF-II has preferential effects on T cell development. Furthermore, it has been shown that the administration of subcutaneous or intravenous IGF-I reduces clinical deficits and lesion severity in experimental allergic encephalomyelitis (EAE), an animal model of MS.

Torres-Aleman et al., reported that serum concentrations of IGF-I and IGFBPs-1 to -4 were not significantly different between patients with MS and controls. In the present study we compared both serum and cerebrospinal fluid concentrations of IGF I, IGF-II, and IGFBPs -1, -2, and -3 between patients with MS and controls.
Material and Methods

Patients and controls

Fifteen patients (nine women and six men; 39 ± 3 years) with MS and 15 sex and age-matched (41 ± 2 years) controls were included in the study. All MS patients received a lumbar puncture as part of their diagnostic work-up. They were classified as clinically or laboratory-supported definite MS according to the criteria of Poser et al. \(^{15}\). Controls were patients without MS who underwent a lumbar puncture as part of a diagnostic work-up. Final diagnosis in controls was strabismus (1), idiopathic dystonia (2), intervertebral disc protrusion (2), multiple cerebrovascular lesions (1), cerebral venous thrombosis (1), and no neurologic disease (8). None of the patients had received corticosteroids within the last month. Blood samples and cerebrospinal fluid was obtained between 0900 and 1200 h. Samples were immediately centrifuged and used for routine examination, and 2–3 ml of serum and cerebrospinal fluid was stored at -80°C and used for this analysis.

Binding assays

IGF-I was determined by a hydrochloric acid-ethanol extraction radioimmunoassay (Nichols Institute Diagnostics, California, USA) \(^{9}\). IGF-II was measured by a non-extractive radioimmunoassay to which an excess of IGF-I was added to avoid interaction with IGFBPs (Mediagnost, Tubingen, Germany) \(^{1}\). IGFBP-1 was determined by a sandwich enzyme immunoassay (Mediagnost; Tubingen, Germany). A two-step system was used by coupling a monoclonal antibody against IGFBP-1 to the microtiter plate, and a second anti-IGFBP-1 monoclonal antibody linked to horseradish peroxidase. IGFBP-2 was measured by a radioimmunoassay (Mediagnost; Tubingen, Germany) based on the method described by Elmlinger et al. \(^{4}\), and IGFBP-3 by a radioimmunoassay (Nichols Institute Diagnostics; California, USA) as described by Strasburger \(^{18}\).

Results and discussion

Statistical analysis was performed by the Mann-Whitney \(U\)-test. A value of \(P < 0.05\) was taken as significantly different. The results are summarised in Table 1. Our results corroborate the findings by Torres-Aleman et al. \(^{19}\) that IGF-I, IGFBPs -1, -2, and -3 concentrations in
sera of MS patients were not different from that in controls. In addition, we found no significant difference in serum IGF-II levels between the two groups.

<table>
<thead>
<tr>
<th></th>
<th>Multiple sclerosis</th>
<th>Controls</th>
<th>*P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I serum</td>
<td>264 ± 18</td>
<td>227 ± 30</td>
<td>0.079</td>
</tr>
<tr>
<td>IGF-I csf</td>
<td>0.95 ± 0.21</td>
<td>0.90 ± 0.13</td>
<td>0.789</td>
</tr>
<tr>
<td>IGF-II serum</td>
<td>875 ± 60</td>
<td>808 ± 44</td>
<td>0.462</td>
</tr>
<tr>
<td>IGF-II csf</td>
<td>19 ± 2</td>
<td>20 ± 2</td>
<td>0.618</td>
</tr>
<tr>
<td>IGFBP-1 serum</td>
<td>1.81 ± 0.40</td>
<td>0.83 ± 0.21</td>
<td>0.095</td>
</tr>
<tr>
<td>IGFBP-1 csf</td>
<td>n.d.</td>
<td>n.d.</td>
<td>-</td>
</tr>
<tr>
<td>IGFBP-2 serum</td>
<td>463 ± 62</td>
<td>444 ± 57</td>
<td>0.962</td>
</tr>
<tr>
<td>IGFBP-2 csf</td>
<td>241 ± 18</td>
<td>201 ± 14</td>
<td>0.172</td>
</tr>
<tr>
<td>IGFBP-3 serum</td>
<td>4460 ± 470</td>
<td>4000 ± 240</td>
<td>0.431</td>
</tr>
<tr>
<td>IGFBP-3 csf</td>
<td>10.6 ± 3.2</td>
<td>11.3 ± 3.3</td>
<td>0.930</td>
</tr>
</tbody>
</table>

All data are expressed in ng/ml. IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; csf, cerebrospinal fluid; n.d., not detectable. *Data were analysed using Mann-Whitney U-test.

In adult rats IGF-I and II appear to cross the blood–brain barrier in only a few restricted brain areas, including the paraventricular nucleus, supraoptic nucleus, and anterior nucleus of the thalamus. Thus, it seems unlikely that under physiological conditions IGFs circulating in blood have a trophic effect on oligodendrocytes, as these large proteins do not sufficiently cross the blood–brain barrier to supply the whole white matter.

The findings of a protective effect of systemically administered IGF-I in EAE may be explained by a disruption of the blood–brain barrier in this animal model, allowing IGFs to concentrate in the inflammatory lesions. Another important mechanism is the ability of IGFs
to affect immune responses, including an inhibition of the migration of lymphocytes into the central nervous system\textsuperscript{10}.

As far as its trophic effects on oligodendrocytes are concerned, the IGF system in cerebrospinal fluid may be more relevant than that in serum. In cerebrospinal fluid IGF-II and IGFBP-2 represented the major components of the IGF system; both proteins are produced and secreted in large amounts by meningeal cells and choroid plexus\textsuperscript{6,7}. IGFBP-3 and IGF-I were present in lower concentrations, and IGFBP-1 was not detectable. We found no significant differences in cerebrospinal fluid levels of IGF-I, IGF-II, IGFBPs-2 and –3 between MS patients and controls (Table 1).

We have previously shown in post-mortem obtained brains that IGF-I receptor densities and binding characteristics in white matter were not different between MS patients and controls\textsuperscript{22}. The results of the present study demonstrate that the IGF systems in serum and cerebrospinal fluid are also unaltered in-patients with MS, at least for the components that we investigated. The important question arises whether the systemic administration of IGF-I, which is available for clinical use, may be useful for the treatment of MS patients. Besides from its putative immunomodulatory activity, we do not expect that systemically administered IGF-I can protect oligodendrocytes and activate myelin formation, unless the blood–brain barrier is disrupted. Although a breakdown of the blood–brain barrier is an early event in MS lesions, the pleiotrophic activity of IGF-I may pose another problem. IGF-I receptors are also present on astrocytes in MS plaques\textsuperscript{22}, and IGF-I has mitogenic effects on cultured astrocytes\textsuperscript{20}. Transgenic mice that overexpress IGFBP-1, which may inhibit the action of IGF-I through IGF-I receptors, showed reduced glial cell proliferation in response to injury\textsuperscript{14}. Therefore, IGF-I may not only protect oligodendrocytes and stimulate remyelination but also enhance the astrogliosis that limits myelin repair. Further research is necessary before administering IGF-I to patients with MS. An interesting approach may consist of using substances that increase the endogenous free levels of IGFs in the central nervous system by displacing them from their binding proteins\textsuperscript{11}, perhaps in combination with substances that inhibit astrocyte proliferation.

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References


