Intravenous immunoglobulin treatment in the prevention of childbirth-associated acute exacerbations in multiple sclerosis: a pilot study

Abstract Acute exacerbations frequently occur after childbirth in patients with relapsing-remitting multiple sclerosis (MS). The present pilot study was initiated in an attempt to reduce the number of childbirth-associated acute exacerbations in the postpartum period. We treated nine MS patients with a history of 12 childbirth-associated acute exacerbations that had occurred 2–9 weeks after previous deliveries. The patients were administered intravenous immunoglobulin (IVIg) at a dose of 0.4 g/kg per day for 5 consecutive days during the 1st week after childbirth and at 6 and 12 weeks thereafter. None of the treated patients relapsed during the 6-month period after delivery. However, three patients had a remote relapse, two at 8 months and one at 10 months after childbirth, but these probably represented the natural course of disease and were not associated with childbirth. We conclude that IVIg treatment may prevent acute childbirth-associated exacerbations in relapsing-remitting MS patients.

Key words Multiple sclerosis • Pregnancy • Intravenous immunoglobulin • Exacerbation

Introduction

In women, multiple sclerosis (MS) mainly occurs during the reproductive years. Frequently, symptoms of the disease do not appear until after childbirth [1]. Several studies had shown that the relapse rate in the year of the pregnancy is significantly higher than in non-pregnant MS patients [2–4]. It has also been shown that a large majority of relapses can occur during the puerperium [5–7]. Although two studies did not confirm an increase in relapse rate in the 6 months following delivery [8, 9], large reviews of the gestational history of 623 women with MS have found the risk of MS onset, exacerbation, or progression to be 2–3 times higher during pregnancy than during pregnancy [10, 11]. It was therefore concluded by Birk and Rudick in a recent extended review [12] that the postpartum period carries a high risk for clinical exacerbations of MS symptoms.

As no therapeutic trials have ever been implemented to prevent exacerbations in the postpartum period of MS patients and since our experience of using intravenous immunoglobulin (IVIg) both in the animal model of experimental autoimmune encephalomyelitis (EAE) [13] and in clinical trials with relapsing-remitting MS patients [14, 15] has been favourable, we conducted the present pilot study. This report provides preliminary results on the effect of IVIg treatment in reducing exacerbations in the postpartum period in relapsing-remitting MS patients.

Patients and methods

Inclusion criteria for participation in the study were: (1) a definite diagnosis of MS [16]; (2) a relapsing-remitting disease course; and (3) a previous history of at least one well-documented acute exacerbation associated with childbirth or spontaneous abortion.

All patients were followed throughout the pregnancy and 1 year after delivery, and were examined neurologically once every 2 months using the Kurtzke Expanded Disability Status Scale (EDSS) [17] during the 2 consecutive years of the study.

None of the patients received corticosteroid therapy and/or other immunosuppressive drugs during pregnancy. None had a history of anaphylaxis after previous transfusions of blood or blood
products; in all patients IgA levels were measured by plasma immunoelectrophoresis. All patients gave their informed consent before participating in the study.

**IVIg treatment**

IVIg (Gamimune N, Miles, Cutter Biological, Promedico, Israel) in a sterile 4.5–5.5% solution of human protein in 9–11% maltose was given intravenously once daily for 5 consecutive days at a dose of 0.4 g/kg per day starting from the first 1–3 days after delivery. Thereafter, patients were further treated with booster doses of IVIg, 0.4 g/kg per day, at 6 and 12 weeks after delivery.

**Evaluation of acute exacerbations**

Patients were seen at times of suspected exacerbations, i.e. when rapid onset of new symptoms or worsening of pre-existing symptoms persisting for 48 h or more was noted. An event was counted as an exacerbation only when the patient’s symptoms were accompanied by observed objective changes at the neurological examination, such that there was an increase of at least one grade in the score for one of the eight functional groups of the Kurtzke EDSS. Patients experiencing an acute exacerbation were evaluated at frequent intervals, usually every week, until a new, stable neurological baseline was established.

For all the patients included in the study, the diagnosis was made in our department and their medical records included data of their previous relapses defined by the same criteria.

**Results**

Nine pregnant MS patients (mean age 30, SD 4.1; range 22–35 years) were included in the study. Disease duration was 5.6, SD 2.5 years (range 3–11 years) and neurological disability evaluated by the Kurtzke EDSS was 3.4, SD 1.6 (range 1.5–6.5) at the beginning of the pregnancy. The total number of previous pregnancies or spontaneous abortions was 12, and each was associated with an exacerbation, yielding a mean exacerbation rate of 1.0 in the postpartum year. The time from childbirth to the occurrence of an exacerbation ranged from 2 to 9 weeks (mean 5.8, SD 2.1 weeks). Table 1 summarizes the clinical data of the patients.

During pregnancy all the patients felt well, except for one who experienced an exacerbation at 15 weeks’ gestation manifested by optic neuritis in her right eye. Other common complaints were urinary frequency and urgency (mostly during the third trimester) and these were considered to be related to the pregnancy itself. All patients gave birth by vaginal delivery, and none developed any obstetrical complications. IVIg treatment was well tolerated and resulted in no major side-effects in any of the patients. One patient complained of dizziness and headaches during the second and third booster-dose treatments.

During the 6 months after delivery none of the patients had a relapse. Three relapses occurred in three patients: 8 months (n = 2) and 10 months (n = 1) after delivery (Table 1).

### Table 1  Effect of IVIg treatment on childbirth-associated acute exacerbations

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at disease onset (years)</th>
<th>Age at pregnancy (years)</th>
<th>Childbirth-associated exacerbations</th>
<th>No treatment</th>
<th>IVIg treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>23</td>
<td>4 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>21&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>30</td>
<td>6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>24</td>
<td>8 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>25</td>
<td>3 weeks</td>
<td></td>
<td>8 months</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>26</td>
<td>6 weeks</td>
<td></td>
<td>9 weeks</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>28</td>
<td>5 months</td>
<td></td>
<td>8 months</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>27</td>
<td>7 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>28</td>
<td>28</td>
<td>9 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Time from childbirth to appearance of an acute exacerbation  
<sup>b</sup> Spontaneous abortion

**Discussion**

IVIg treatment given after delivery prevented acute exacerbations in the postpartum period. None of the nine MS patients treated experienced a relapse during the 6 months after childbirth, while each had a previous history of at least one acute exacerbation associated with childbirth or spontaneous abortion. The three relapses that occurred 8 and 10 months after delivery probably represent the natural course of disease and are not associated with childbirth.

As the half-life of IVIg is 18–20 days, it can be estimated that after 100 days there is no drug in the serum, although its modulatory effects on the immune system might persist. It would be of interest, however, to establish whether additional IVIg booster doses could have prevented the exacerbations in the three patients who relapsed, as in previous studies we reported a significant reduction in acute exacerbations in relapsing-remitting MS patients treated with IVIg for 1–3 years [14, 15]. Although the rationale for IVIg treatment in MS should be further confirmed, the present study provides additional