CASE REPORT

Relapsing-remitting multiple sclerosis and chronic idiopathic neutropenia: a challenging combination

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SUMMARY

We report the challenges of treating relapsing-remitting multiple sclerosis (MS) in a 31-year-old woman with long-standing chronic idiopathic neutropenia. The treatment with the disease-modifying therapy interferon- β was significantly complicated by a further fall in her generally low neutrophil count, to values below $0.5 \times 10^9/l$, although this recovered rapidly when the treatment was stopped. We discuss the difficulties of balancing the risk of neutropenia with a risk of MS relapse.

BACKGROUND

We report the case of a woman with chronic idiopathic neutropenia (CIN), who developed relapsing-remitting multiple sclerosis (MS), and whose disease-modifying treatment was complicated by her low neutrophil count. In MS, an autoimmune inflammatory response causes demyelinating lesions in the central nervous system, leading to neurodegeneration. The current first-line treatments for the relapsing-remitting type of MS are immunomodulating medications such as interferon- β (BIFN), which aim to reduce the frequency of relapses. CIN may be caused by autoantibodies against neutrophils leading to increased neutrophil destruction and decreased blood neutrophil numbers, yet patients usually remain asymptomatic.¹ It has previously been associated with MS in one published case report.²

CASE PRESENTATION

A 31-year-old British Caucasian woman presented to the neurology clinic in 2010 with symptoms suspicious for MS. She had developed an altered sensation starting in her perianal region, radiating down to her thighs and around her buttocks, and then spreading to both the legs and up to her umbilicus over a few days. She had difficulty in walking because of her leg weakness and also reported some difficulty in voiding urine. Two months earlier, she described a similar gradual onset of an altered sensation only in her right leg, which had persisted for 10 days. She was admitted to the neurology unit for investigation.

In her history, in 2005, she experienced a profound burning sensation on her left forehead and cheek, stopping at the upper lip, with no rash. A tentative diagnosis of shingles was made by her family doctor, it was treated with antiviral medication and it settled after 1 week. In 2007, she developed one-sided eye pain that persisted only during eye movement, with no change in visual acuity and

which again resolved within 1 week without seeking any medical advice.

The patient was otherwise healthy and was not taking any medication. She was born and raised in Northern Ireland. The only history of note was one of neutropenia, which had first been noticed in 2006. On several occasions, her neutropenia was recorded at around $1.0 \times 10^9/l$ (figure 1A); she was investigated for this in 2009, but had normal blood film, haematinics, immunoglobulin analysis, negative routine autoantibodies (rheumatoid factor and antinuclear antibodies) and a normal chest x-ray, and CIN was diagnosed. Antibodies to leucocytes were not measured, as this is not a routine local test for asymptomatic patients. As a child, she did not suffer more infections than normal. There was no family history of MS or blood disorders.

Neurological examination revealed normal tone, a paraparesis (left leg Medical Research Council (MRC) grade 4/5; right leg MRC grade 5/5) and symmetrical brisk reflexes. She had an altered sensation to all the modalities bilaterally in the legs extending to the thoracic level 10 (T10) level. The examination of the upper limbs and the cranial nerves was normal, notably with normal fundoscopy and visual acuity.

On examination her urea and electrolytes, glucose, liver function tests, erythrocyte sedimentation rate, vitamin B₁₂, folate, thyroid function tests and calcium were normal and rheumatoid factor and antinuclear antibodies were negative. Her full blood count was normal except for a borderline low neutrophil number. An MRI of her brain and spine both showed abnormalities. There were several high T2 signal lesions in the cerebellar white matter (figure 1B), with the largest lesion located within the splenium of the corpus callosum and the adjacent right parietal white matter (figure 1B, I–III). Several other small white matter lesions were found in the body of the corpus callosum and in the periventricular and subcortical white matter (figure 1B, IV–VI). Infratentorial white matter lesions were also noted, especially in the left pons and left middle cerebellar peduncle. In the spinal cord, there were scattered lesions at the level of C (cervical) 2, T3, T4 and T11 (not shown). The MRI findings were consistent with demyelination. At this point, a clinically isolated syndrome was diagnosed, because of the uncertainty over the cause of the neurological episodes in 2005 and 2007, and she received a 3-day course of methylprednisolone (500 mg orally, twice daily). Of note, her neutrophil count increased to $2.20 \times 10^9/l$ following treatment with steroids, supporting her

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Figure 1 (A) Table of blood counts. (B) MRI scans of the patient's brain in the sagittal (I, II, IV and V) and transverse (III and VI) view indicating white matter lesions (some indicated with arrows). (C) Graph showing patient's neutrophil count during various treatment attempts.

haematological diagnosis. In the following 4 weeks her walking improved, but it took 5–6 months until full recovery, except for persistent numbness in her feet.

In 2011, she was presented to the clinic again with a sensory relapse. She reported hypersensitivity in her right axilla, which over 1 week progressed to decreased sensitivity in her right leg reaching up to the bottom of her rib cage. She received another 3-day course of methylprednisolone as before; her symptoms settled down over the following month and a diagnosis of relapsing-remitting MS was made. Since the patient had two significant relapses within 2 years, she fulfilled the UK guidelines for disease modifying medication. In August 2011, she was started on 0.25 mg BIFN 1 β subcutaneous injections on alternate days (Extavia) with the aim to reduce occurrence of future relapses.

After 9 weeks of Extavia treatment, her neutrophil count decreased to $0.55 \times 10^9/l$ (figure 1C) and her Extavia therapy was discontinued. After 2 weeks her neutrophil count recovered, and we restarted Extavia, resulting in similar low neutrophil counts within 2 weeks. She was then given Rebif (BIFN 1 α) as

this is manufactured in a low dose formulation (22 mcg, 3/week), which we hoped would have less impact on her neutrophils. Throughout this time, she remained entirely fit and well. While on Rebif, her neutrophil count decreased again to a nadir of $0.49 \times 10^9/l$, but based on the advice from the haematological test results her treatment was continued. Her neutrophils increased to below normal, and we increased her Rebif to a higher dose (44 mcg, 3/week) in March 2012. This caused another drop in her neutrophil level to $0.75 \times 10^9/l$, but not any further decrease, and she has remained on this, relapse-free, with no other problems. On all occasions, the rest of her full blood count has been normal.

DISCUSSION

BIFN is one of the first anti-inflammatory agents and immunomodulators approved for the treatment of relapsing-remitting MS, and remains a therapeutic mainstay. There are two types of BIFN used therapeutically, BIFN 1 α and 1 β , and both show a reduction of relapses by approximately 30%.^{3 4}

The mechanism of reduction of MS relapses by BIFN is not fully understood, but it may involve inhibition of T-lymphocyte proliferation and decreased production of interferon- γ ,⁵ increased expression and concentration of anti-inflammatory cytokines⁶ and inhibition of major histocompatibility complex class II expression, leading to reduced antigen presentation in the central nervous system.⁷ BIFN may also help to re-establish and reduce inflammatory cell trafficking across the blood brain barrier⁸ and increase nerve growth factor production potentially aiding neuronal survival and repair.⁹

BIFN therapy can cause mild suppression of the bone marrow leading to anaemia, leukopenia and thrombocytopenia. A drug safety study in 2004 showed that two-thirds of patients receiving the BIFN treatment developed cytopenias within 6 months of starting the therapy. Changes were seen predominantly in the total white blood cell count and neutrophil number. Generally, these cytopenias resolved within 3–4 months of the therapy, and only a very small number of patients (6 of 727; 0.8%) stopped their treatment owing to haematological abnormalities.¹⁰ As our patient had pre-existing CIN, her neutrophil count was already low before starting the BIFN treatment. Upon BIFN therapy, she developed profound (yet asymptomatic) neutropenia within 2 weeks and exhibited rapid recovery after the treatment cessation. Restarting the therapy caused the same effect, suggesting causality rather than coincidence. There was no evidence for bone marrow failure. Her neutrophil count stabilised in the below normal range initially on a lower dose therapy and now also on a full dose BIFN. We considered using glatiramer acetate instead of BIFN, as this is not known to cause neutropenia. Although the REGARD¹¹ and the BEYOND¹² studies suggested equal efficacy of BIFN and glatiramer acetate in terms of time to the next relapse, the BIFN-treated patients in the REGARD study had fewer gadolinium enhancing lesions on MRI scans. We discussed this evidence with the patient (who is a research scientist) and decided to continue with BIFN, keeping glatiramer acetate as a reserve.

Neutropenia poses a challenge in the treatment of relapsing-remitting MS; however, the causative mechanisms remain unclear. We aimed to balance the risk of MS relapses against profound (albeit asymptomatic) neutropenia. The PRISMS trial¹³ suggested that the full-dose BIFN showed a trend to being more effective than the half-dose BIFN (0.11 less mean relapses per patient after 2 years) and we are currently successfully treating our patient on this dose (by slow dose escalation), with the aim of reducing her chance of further relapses, but maintaining her neutrophil count in an acceptable range, which we have set (arbitrarily) at above $0.5 \times 10^9/\text{l}$. In the previous reported case of MS and CIN, granulocyte colony stimulating factor and γ -globulin were used to stimulate neutrophil numbers (2), but we have not yet needed to consider this in her case.

Learning points

- Concurrent diagnoses of chronic idiopathic neutropenia (CIN) and multiple sclerosis (MS) are uncommon.
- Treatment of relapsing-remitting MS with interferon- β (BIFN) poses a challenge in a patient with CIN.
- Using a slow dose escalation of BIFN allows titration of neutrophil numbers.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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