CASE REPORT

CANOMAD responding to weekly treatment with intravenous immunoglobulin (IVIg)

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Accepted 21 March 2014

SUMMARY

A 48-year-old man presented with numbness in fingers and diplopia 1 week after a flu-like illness. He made a full recovery but 8 years later developed progressive and disabling sensory ataxia. He had superimposed acute flare-ups with numbness, double vision and ptosis, all following infections. A blood test showed antidisialosyl antibodies including GD1b, GD3, GT1b and GQ1b in keeping with the diagnosis of chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins and antidisialosyl antibodies (CANOMAD). Initial treatment with monthly courses of intravenous immunoglobulin (IVIg) 0.4 g/kg/day for 5 days every 4 weeks helped temporarily but there were marked disabling fluctuations of symptoms. With IVIg 0.6 g/kg/day weekly his symptoms are stable. He remains mobile and has no eye symptoms without need for any other medication. This case demonstrates that weekly IVIg infusions instead of one 5-day course monthly may be able to avoid fluctuations of symptoms in CANOMAD.

BACKGROUND

CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins and antidisialosyl antibodies) has previously been described as a rare chronic neuropathy comprising sensory ataxia, absent tendon reflexes and preserved power in the limbs. Motor weakness predominantly affects oculomotor and bulbar muscles, clinically reminiscent of Miller Fisher syndrome (MFS).¹

Additionally, CANOMAD implies a typical pattern of laboratory features, such as benign IgM paraproteinaemia with antibodies including GD1b, GD3, GT1b and GQ1b. A remarkable amount of these antibodies was identified as cold agglutinins.¹

Electrophysiological as well as histopathological investigations show signs of demyelinating and axonal damage. Patients with CANOMAD are usually severely disabled by their symptoms, in particular sensory ataxia. Immunosuppressive treatment, intravenous immunoglobulin (IVIg) and plasma exchange have been used but there are no randomised trials.¹

To the best of our knowledge, this is the first reported case which demonstrates that weekly infusions of IVIg instead of one 5-day course monthly may be able to avoid peaks and troughs of symptoms in CANOMAD.

CASE PRESENTATION

A 48-year-old man, working as a maintenance supervisor, was referred to hospital by his general

practitioner as an emergency because of subacute neurological symptoms. One week prior to admission the patient felt unwell, having a sore throat, swollen lymph nodes and associated fever. Shortly before his admission he had additionally developed numbness in his finger tips and double vision. On examination the patient had diplopia. He had gait ataxia and limb ataxia predominantly on the right and impaired joint position sense. There was no muscle weakness in the limbs. His tendon reflexes were all absent.

His medical history was unremarkable and he did not need any regular medication.

At this stage the diagnosis of MFS was made and as expected, the patient made a prompt and full recovery and was discharged. Eleven years later he was referred to the neurologist as an outpatient, now at age 59. This time he had a more chronic presentation with marked and increasingly disabling sensory ataxia. The symptoms had slowly progressed over the past 3 years. At this time the vitamin B₁₂ levels were 189 ng/L (180–914). Nevertheless, he was treated with hydroxocobalamin 1 mg intramuscularly every other day for 2 weeks followed by two monthly injections without any benefit. We did not test for antiparietal cell and intrinsic factor antibodies.

Several months later, the patient presented with a second acute flare-up of his neurological symptoms consisting of increased ataxia and ophthalmoplegia, again following an infection but described as even worse compared with the first acute manifestation. However, he recovered sufficiently enough to go back to work. His symptoms were stable for approximately 1 year, when the sensory ataxia and the signs of neuropathy deteriorated noticeably.

At that time, a blood test for specific antibodies had been arranged and antidisialosyl antibodies including GD1b, GD3, GT1b and GQ1b as well as IgM paraprotein were detected, leading to the diagnosis of chronic ataxic neuropathy with antidisialosyl IgM antibodies. This condition had previously been described by the acronym CANOMAD, a disease reminiscent of MFS.¹

INVESTIGATIONS

In this patient, a CT scan of the brain was normal. Analysis of cerebrospinal fluid (CSF) was entirely normal after his first acute manifestation but showed a non-specific elevation of protein 1.01 g/L (0.1–0.45), IgG 0.079 g/L (0.007–0.035) and albumin 0.75 g/L (0.07–0.35) 12 years later.

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To cite: Krenn M, Keir G, Wieshmann UC. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-202545

Neurophysiological investigations demonstrated absent sensory nerve action potentials in median, ulnar, radial, peroneal and sural nerves. The motor nerve action potentials and the nerve conduction velocity were slightly low and the tibial F wave latency was prolonged.

A blood test showed elevated levels of IgM with an IgM λ monoclonal gammopathy as well as the typical pattern of anti-ganglioside antibodies (GD1b, GT1b, GQ1b, GD3 and GM3), fitting in with the diagnosis of CANOMAD.

Our patient's titres of CANOMAD-specific antibodies were documented as follows:

GD1b IgM > 1/12 500 (< 1/500)

GT1b IgM > 1/12 500 (< 1/500)

GQ1b IgM > 1/12 500 (< 1/500)

GD3 IgM > 1/12 500 (< 1/500)

GM3 IgM > 1/12 500 (< 1/500)

DIFFERENTIAL DIAGNOSIS

Prior to the detection of the anti-ganglioside antibodies, the differential diagnosis included vitamin B₁₂ deficiency, copper deficiency, tabes dorsalis, HIV, neuroborreliosis and sarcoidosis but none were clinically likely diagnoses. Vitamin B₁₂ and copper deficiency are often associated with anaemia but neither causes an ophthalmoplegia. Syphilis, HIV and neuroborreliosis show raised cell counts in CSF and the patients usually have a history of sexually transmitted disease or tick bites.

MFS and Guillain-Barré syndrome (GBS) are by definition acute neuropathies, and chronic inflammatory demyelinating polyneuropathy (CIDP) does not cause ophthalmoplegia.

TREATMENT

After diagnosing CANOMAD, the patient was treated with monthly courses of IVIg (Intratect) 0.4 g/kg/day for 5 days every 4 weeks and prednisolone 30 mg on alternate days and azathioprine 200 mg a day.

Although our patient clearly benefited from IVIg in the first 2 weeks after the infusion, his symptoms were overall only poorly controlled. He had a severe deterioration of his sensory ataxia and ophthalmoplegia the week before the next course of IVIg, rendering him a wheelchair user. He even suffered a third flare-up following flu-like symptoms. Prednisolone and azathioprine were added in an attempt to iron out the peaks and troughs but were not effective. He was on this treatment regimen for 2 years. The patient suggested spreading out the infusions of IVIg over the month. In view of the short half-life of IVIg we decided somewhat arbitrarily on weekly infusions. We could have decided on infusions every 2 weeks or every 10 days but weekly infusions were most practical.

OUTCOME AND FOLLOW-UP

With IVIg (Privigen) 0.6 g/kg/day weekly the symptoms are now stable for more than 2 years. He has only minimal non-disabling eye symptoms. He has sensory ataxia but he is independently mobile inside the house, although he prefers to walk outdoors with his wife. He feels that he is overall on a very slow downward trajectory. Prednisolone and azathioprine were successfully phased out 2 years ago and no further immunosuppressive treatment is necessary at the moment.

To illustrate the treatment response we used the Overall Disability Sum score (ODSS) in order to assess the clinical benefit of the change in our treatment regimen.² The ODSS is a scale from 0 (no signs of disability) to 12 (maximum disability). During the monthly courses of IVIg the symptoms had deteriorated gradually after one course of infusions and had been worst

just before the next cycle of treatment. Shortly before the regimen change, his arm disability scale was 3 (range 0–5) and his leg disability scale was 6 (range 0–7), resulting in an ODSS of nine. Compared to now, his arm disability scale has improved to 2 and his leg disability scale to 4, leading to an overall score of 6.

It is important to take into account that this score does not comprise eye symptoms due to ophthalmoplegia in CANOMAD, which also could be improved significantly after spreading the IVIg infusions.

DISCUSSION

CANOMAD is a very rare disease within the group of paraproteinaemic neuropathies. Approximately 30 cases have been reported in the existing literature. An association between paraproteinaemic neuropathy and anti-ganglioside antibodies was first described in 1985.³

CANOMAD presents with a typical pattern of clinical and serological features, which has been delineated by Willison *et al*¹ in a series of 18 patients. It was shown that it predominantly occurs in men with a median age of onset of 53 years. The clinical main feature is a chronic sensory ataxic neuropathy with superimposed relapsing-remitting symptoms such as ocular, sensory or bulbar manifestations. Another frequent symptom is pseudoathetosis—involuntary and writhing movements on eye closure as a consequence of joint position sense impairment. The patient presented in our report still shows pseudoathetosis and sensory ataxia, whereas his ocular symptoms have diminished significantly due to successful treatment.

A consistent laboratory feature is a high titre of antibodies against gangliosides with disialosyl groups, namely GD3, GT1b, GD1b and GQ1b.¹ In our patient's serum, all four were found, leading to the correct diagnosis.

Neurophysiological investigations also support the diagnosis of CANOMAD. In nerve conduction studies, sensory responses are commonly unrecordable or at least reduced in amplitude. Willison *et al*¹ found motor abnormalities in over 50% of the cases. Some of the patients showed signs of demyelination. Our case describes absent sensory responses throughout and relatively preserved motor function.

Neuroimaging, in particular MRI of the brain, can result in a broad spectrum of pathological signs including ischaemic lesions, generalised atrophy and central white matter demyelination.¹ There is no MRI scan of our patient available. A CT scan of the head was documented as normal 11 years after his first acute presentation.

The course of CANOMAD usually extends over decades but is very variable. Some patients are wheelchair users after 9 years, whereas others are mobile after 29 years.¹ Owing to the fluctuating nature and the variability between patients with CANOMAD, it is extremely difficult to assess the effectiveness of treatment. Our observation suggests that giving IVIg weekly is more effective than just every 4 weeks, despite using a very similar dose. We clearly and repeatedly observed worsening of the patient's symptoms prior to the following course of IVIg when given every 4 weeks. His symptoms were so severe that he became a wheelchair user. With weekly infusions of IVIg these fluctuations could be avoided and he still remains mobile with two sticks. We think that these observations cannot be explained by natural fluctuations of the disease. According to some case reports, IVIg, plasma exchange and immunosuppressive drugs were able to improve CANOMAD, but there is still no evidence-based treatment. In the majority of documented cases, including

ours, a deterioration of symptoms was stated after initial response to this treatment.^{4–7}

A recent paper also suggested that an individual adjustment of IVIg intervals and doses in CIDP and myasthenia gravis (depending on the patient's clinical condition) could help to improve the treatment outcome.⁸

In general, IVIg treatment is well known for its anti-inflammatory effects in several medical conditions with entirely different pathomechanisms. For instance, IVIg was shown to reduce complement uptake in GBS, whereas in CIDP it might up-regulate the low-affinity inhibitory receptor FcγRIIB on effector macrophages contributing to its anti-inflammatory effect. Among others, there may also be anticytokine as well as direct autoantibody neutralising effects.⁹

It is impossible to know which mechanism is the most important in our patient. The fact that he has a profound but short-lasting benefit could be in keeping with a direct autoantibody neutralising effect. Antibody neutralisation by IVIg would almost instantly prevent further binding to myelin thus improving nerve function but this effect would be short lasting because of the short half-life of IVIg.

Three case reports to date have suggested that the use of the anti-CD20 antibody rituximab could be effective when other treatment options have failed. That fact leads to the assumption that IgM antibodies in CANOMAD play a crucial role in the pathogenesis of the disease.^{5–7}

Up to now, treatment with the anti-CD20 antibody rituximab has not been tried in our patient, since the current treatment has been sufficient to stabilise the disease so far. As this is a relatively new drug, the long-term side effects are still not completely elucidated. In our case, it was also obvious that IVIg as our first treatment option showed promising clinical effects, even after monthly administration, but they were only short lasting and fluctuating in nature. As a consequence, a weekly regimen appeared to be a logical and entirely safe alternative and was thus an option worth trying in our patient. The add-on of another drug would automatically have led to a higher risk of adverse effects. Assessing the patient's condition after the regimen change also showed enough response to abandon further treatment options for the present. Nevertheless, rituximab might still be an option definitely worth considering in the case of deterioration of symptoms.

A possible advantage of a treatment regimen including rituximab and IVIg is the fact that it combines more molecular mechanisms of work at once, potentially leading to synergistic effects. Even though discussed controversially in the recent literature, rituximab has also shown to be effective in some patients with the related condition CIDP.¹⁰

It is however essential to take into account that the current understanding of CANOMAD and its treatment options is merely based on few case descriptions. Until now, none of the regimens can be used according to evidence-based knowledge.

Generally, the pathogenesis of CANOMAD and therapeutic mechanisms is still poorly understood. Overall, undoubtedly

there is a lack of data on CANOMAD treatment, mainly caused by its low prevalence. Randomised trials would be essential in order to optimise therapeutic approaches in this rare condition.

Learning points

- ▶ In patients with chronic sensory ataxic neuropathy and ophthalmoplegia screening for antiganglioside (glycolipid) antibodies is helpful to diagnose chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins and antidiasialosyl antibodies (CANOMAD).
- ▶ CANOMAD may be misdiagnosed initially as the monophasic Miller Fisher syndrome. Delays in the diagnosis can occur.
- ▶ In CANOMAD, weekly infusions of intravenous immunoglobulin instead of one 5-day course monthly might be able to avoid fluctuations of symptoms.

Acknowledgements The author would like to thank Carol Chadwick for proofreading the document.

Contributors MK wrote the manuscript. GK gave advice regarding the immunological findings. UCW suggested the case report and reviewed the manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Willison HJ, O'Leary CP, Veitch J, *et al.* The clinical and laboratory features of chronic sensory ataxic neuropathy with anti-disialosyl IgM antibodies. *Brain* 2001;124(Pt 10):1968–77.
- 2 Merkies IS, Schmitz PI, van der Meche FG, *et al.* Clinimetric evaluation of a new overall disability scale in immune mediated polyneuropathies. *J Neurol Neurosurg Psychiatry* 2002;72:596–601.
- 3 Ilyas AA, Quarles RH, Dalakas MC, *et al.* Monoclonal IgM in a patient with paraproteinemic polyneuropathy binds to gangliosides containing disialosyl groups. *Ann Neurol* 1985;18:655–9.
- 4 Kam C, Balaratnam MS, Purves A, *et al.* Canomad presenting without ophthalmoplegia and responding to intravenous immunoglobulin. *Muscle Nerve* 2011;44:829–33.
- 5 Loscher WN, Woertz A, Wallnofer M, *et al.* Successful treatment of CANOMAD with IVIg and rituximab. *J Neurol* 2013;260:1168–70.
- 6 Siddiqui K, Cahalane E, Keogan M, *et al.* Chronic ataxic neuropathy with cold agglutinins: atypical phenotype and response to anti-CD20 antibodies. *Neurology* 2003;61:1307–8.
- 7 Delmont E, Jeandel PY, Hubert AM, *et al.* Successful treatment with rituximab of one patient with CANOMAD neuropathy. *J Neurol* 2010;257:655–7.
- 8 Broyles R, Rodden L, Riley P, *et al.* Variability in intravenous immunoglobulin G regimens for autoimmune neuromuscular disorders. *Postgrad Med* 2013;125:65–72.
- 9 Gelfand EW. Intravenous immune globulin in autoimmune and inflammatory diseases. *N Engl J Med* 2012;367:2015–25.
- 10 Benedetti L, Briani C, Franciotta D, *et al.* Rituximab in patients with chronic inflammatory demyelinating polyradiculoneuropathy: a report of 13 cases and review of the literature. *J Neurol Neurosurg Psychiatry* 2011;82:306–8.

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