CONCISE REPORT

Intravenous immunoglobulins in peripheral neuropathy associated with vasculitis

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Background: Peripheral neuropathy is a prominent feature of the systemic and secondary vasculitides. Usually, it is responsive to corticosteroids, but in certain cases it may be resistant to corticosteroid or immunosuppressive treatment, or both.
Objective: To present patients who exhibited various inflammatory diseases accompanied with vasculitic peripheral neuropathies for which intravenous immunoglobulin (IVIg) was used for treatment.
Methods: Six patients with Sjögren's syndrome, systemic lupus erythematosus (SLE), vaccination induced vasculitis, Churg-Strauss vasculitis, mixed cryoglobulinaemia associated with hepatitis C infection, or sarcoidosis were included. All developed vasculitic peripheral neuropathy, and were treated with high dose IVIg (2 g/kg body weight). The patients were followed up for 1–5 years after this treatment.
Results: In four patients (Sjögren's syndrome, Churg-Strauss vasculitis, SLE, and vaccination induced vasculitis) the neuropathy resolved after IVIg treatment.
Conclusion: IVIg may be beneficial in cases of resistant vasculitic peripheral neuropathy. IVIg should probably be considered as a sole or adjuvant treatment for patients with contraindications to conventional treatment, or alternatively, for patients in whom conventional treatment has failed.

Peripheral neuropathy is a prominent feature of diverse systemic and secondary vasculitides. In patients with mononeuritis multiplex, vasculitis of the vasa nervorum results in neuronal deficits. Patients with vasculitis restricted to the peripheral nervous system are usually responsive to combined treatment with high dose corticosteroids, plasmapheresis, and cyclophosphamide.[1]

Intravenous immunoglobulin (IVIg) is increasingly used in neurological manifestations of autoimmune diseases.[2] However, only a few case reports have discussed the administration of IVIg in patients with vasculitis and peripheral neuropathy who were unresponsive to conventional treatment.[3 4] Here, we describe our experience with IVIg treatment in six patients with peripheral neuropathy due to vasculitis that was unresponsive to conventional immunosuppressive treatment.

CASE REPORTS

Systemic lupus erythematosus

A 12 year old girl was admitted after a convulsive episode. Two weeks earlier she had developed fever, arthralgias, facial rash, hair loss, abdominal pain, and a sensation of burning and painful legs. Our examination noted mainly neurological findings: anxiety, agitation, confusion with memory impairment, and a fine tremor. Muscular strength had decreased with increased sensitivity to touch. Fundus examination was compatible with retinal vasculitis.

The serological analysis disclosed a high positive antinuclear antibody titre, anti-dsDNA, anti-Sm, and anti-Ro antibodies. Lumbar puncture, brain single photon emission computed tomography, brain computed tomography, and magnetic resonance imaging were compatible with central nervous system involvement. Nerve conduction velocity was compatible with peripheral neuropathy.

The patient was diagnosed as having systemic lupus erythematosus (SLE) with active central and peripheral nervous system involvement together with haematological and skin organ involvement. A three day course of intravenous methylprednisolone was started, 1 g every day followed by 20 mg intravenous methylprednisolone three times a day for a week, followed by prednisone 20 mg three times a day. Two weeks later, she remained in agony with unbearably painful legs which did not respond to narcotic drugs. At this point, we decided to institute high dose IVIg at a dose of 2 g/kg body weight given in two days (Omrigam; Tel Hashomer, Israel). The day after, a dramatic response was noted, with a significant decrease in her agonising pain. Gradually her depression, agitation, and confusion improved. Two months later, she was back at school, and maintained with low dose prednisone, hydroxychloroquine, and cyclophosphamide.

Mixed cryoglobulinaemia type II associated with hepatitis C infection

A 67 year old man with type II mixed cryoglobulinaemia associated with hepatitis C infection with severe symmetrical sensorimotor polyneuropathy was referred for assessment. For six years the patient had had distal motor and sensory deficits. On examination, symmetric hyperaesthesia and hyperglasia were found along with bilateral loss of vibration and position sense and loss of ankle jerks. Nerve conduction studies were consistent with a severe sensorimotor polyneuropathy. Treatment with prednisone, interferon alfa, cyclosporin, and pulse cyclophosphamide did not help. IVIg treatment (Pentaglobin; Biotest, Germany: 38 g/l IgG, 6 g/l IgM, and 6 g/l IgA) was instituted 400 ml/day for three days. The patient was treated with two monthly courses, but no clinical benefit was seen.

Sjögren's syndrome

A 41 year old man was admitted with Sjögren's syndrome (SS) associated with agonising distal hand and leg pains. Neurophysiological studies showed a distal, chronic, axonal, demyelinating, and mainly sensory neuropathy. Right leg

Abbreviations: EMG electromyography, ; IVIg, intravenous immunoglobulin; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome

sural nerve biopsy demonstrated mononuclear infiltrates around the vasa nervorum, with ischaemic nerve injury consistent with vasculitis. Treatment with corticosteroids and methotrexate was started but the distal hyperaesthesia and cramps were aggravated. Upon referral, hypertension and diabetes mellitus were discovered and, therefore, the corticosteroid dose was tapered and IVIg treatment was started (Pentaglobin; Biotest, Dreieich, Germany). His symptoms improved gradually. The clinical improvement lasted for three months. Four additional cycles of IVIg treatments were instituted (two with Pentaglobin; two with Omrigam) every 4–6 months. His current clinical improvement is accompanied by normalisation of neurophysiological studies.

Peripheral localised neuropathy after influenza vaccination

A 64 year old man developed peripheral neuropathy one month after an influenza vaccination. The electromyography (EMG) studies demonstrated axonal and motor neuropathy of the right ulnar nerve. Treatment with non-steroidal anti-inflammatory drugs, corticosteroids and azathioprine did not help. One course of high dose IVIg treatment (2 g/kg body weight Omrigam) was given. A week later a dramatic improvement of the right hand function was noticed. His symptoms resolved completely. A repeat EMG was normal.

Sarcoidosis

A 41 year old female patient was diagnosed with sarcoidosis affecting her lungs and liver, 12 years before the referral. The patient was treated with prednisolone and methotrexate.

For 10 months before admission she complained of a severe numbness and cramps in both legs. Neurophysiological studies confirmed a distal, chronic, axonal, demyelinating, and mainly sensory neuropathy. Right leg sural nerve biopsy demonstrated mononuclear infiltrates around the vasa nervorum with an ischaemic nerve injury consistent with vasculitis. Two courses of Pentaglobin 400 ml/day for three days (Biotest) were given, but there was no change in the clinical or neurophysiological studies after a few months of follow up.

Churg-Strauss vasculitis

A 47 year old man with Churg-Strauss vasculitis was admitted with a subacute onset of distal paraesthesias and progressive weakness in the arms and legs. On examination discrete proximal muscle weakness in the arms and legs, with severe distal muscle wasting of the arms, hyporeflexia, and touch-temperature-pain hypaesthesia in a stocking and glove pattern were noted.

Neurophysiological studies were consistent with a symmetrical sensorimotor polyneuropathy. Histological investigations of a skin lesion demonstrated cutaneous necrotising vasculitis with eosinophilic infiltrates.

High dose prednisolone (1 mg/kg body weight) was given for six months with no apparent response, and then gradually tapered to a maintenance dose of 12.5 mg/day. Two months after steroid administration, cyclophosphamide was added (2 mg/kg every day) for nine months with no adequate response. Six cycles of high dose IVIg treatment, 2 g/kg body weight (ISIVEN; Instituto Sierovaccinogeno, Italiano ISI SpA, Italy) were instituted. The patient gradually regained his normal weight and progressive neurological improvement was also seen. The paraesthesias, hypaesthesia, and muscle weakness markedly improved. The laboratory tests and nerve conduction velocity measures returned to normal.

DISCUSSION

In this study we describe six patients with peripheral neuropathy associated with vasculitis. Two of the patients had an acute peripheral neuropathy and the other four had a chronic peripheral neuropathy. All the patients had severe disease with vasculitic peripheral neuropathy which did not responded to corticosteroids and/or cytotoxic drugs, and therefore IVIg was initiated. The dose of IVIg was the regular high intravenous dose: 2 g/kg body weight per cycle of treatment, or Pentaglobin five ml/g a day (38 g/l IgG, 6 g/l IgM, and 6 g/l IgA) for three consecutive days. We followed up the patients by noting clinical subjective improvement, by EMG tests, and by serological and laboratory investigations.

Four of the patients responded to this treatment, including the two patients with the acute forms of the disease, but the patients with sarcoidosis and with mixed cryoglobulinaemia did not respond.

IVIg has become increasingly used in patients with autoimmune and systemic inflammatory diseases.[5–7] In this communication we have extended the experience of IVIg treatment in patients with vasculitic peripheral neuropathy.

Systemic vascular injury is common in SLE. Although peripheral neuropathies occur in 6–28% of patients with SLE, vasculitis is present histologically in just a small proportion of those neuropathies.[8] We treated our patient with SLE with IVIg owing to her central nervous system involvement[9]; interestingly a dramatic improvement was also noticed in her peripheral neuropathy. The girl was treated for two weeks with high dose steroids with no reduction in the agonising pain due to the peripheral neuropathy, and she had an immediate and dramatic response the day after IVIg treatment was started. The cyclophosphamide was given a week after the IVIg, while she was already in a remission from her painful neuropathy. Therefore it seems that the IVIg led to the change in her neuropathy.

Peripheral neuropathies are prominent in SS with a prevalence that ranges from 10 to 50%.[10 11] There are two case reports of such patients in which IVIg was of benefit. In contrast with our patient, whose improvement was gradual, the reported patients had a prompt response to IVIg.[4 12] Another presented patient in this series had severe peripheral neuropathy due to type II mixed cryoglobulinaemia associated with hepatitis C infection. This disease is strongly associated with peripheral neuropathy.[13] Our patient was treated with interferon, cyclosporin, and cyclophosphamide without improvement, yet two monthly courses with IVIg treatment did not lead to a remission.

The presented patient who developed localised mononeuritis after influenza vaccination emphasises the association between vaccination and autoimmunity.[14] The patient's symptoms resolved completely after one course of IVIg treatment. This was not the case in the patient with longstanding sarcoidosis with a rare involvement of a peripheral distal neuropathy.[15]

The last patient was treated with high dose IVIg after 11 months' treatment with steroids and cyclophosphamide. At that point no improvement was noted in his agonising pains due to the peripheral neuropathy. About two months after the initiation of the IVIg treatment the peripheral neuropathy improved. Improvement continued alongside the IVIg treatment. A contribution of the previous treatment cannot be ruled out, but it seems that the IVIg had a pivotal role in the improvement.

The beneficial effects of IVIg in our four patients are most probably multifactorial acting through complement deactivation, receptor blockade, anti-idiotypes, and modulation of cytokine production. In our communication, patients were more likely to remit if they were treated during an acute or subacute phase, in contrast with those who were treated after

a longstanding disease. In all the patients IVIg was found to be safe and did not cause any adverse effect.

In conclusion, our series shows that IVIg may be beneficial in vasculitic peripheral neuropathy, especially in acute multisystem diseases such as SLE and SS. IVIg may be considered as a sole or as adjuvant treatment, particularly in patients for whom other immunosuppressive treatment has failed.

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