Devic’s Neuromyelitis Optica Treated with Intravenous Gamma Globulin (IVIG)

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ABSTRACT: Background: Devic’s syndrome is a demyelinating disease of the spinal cord and optic nerves. It tends to have a poor prognosis, probably due to the occurrence of necrosis within lesions. There is no proven effective treatment although relapses are commonly treated with corticosteroids and people with recurrent attacks may be managed with chronic immune suppressing treatments. Intravenous gamma globulin (IVIG) and plasma exchange are reasonable treatment options because Devic’s syndrome is believed to be antibody mediated. We report two patients of Devic’s syndrome that stabilized following initiation of monthly IVIG. Patient 1: A 42-year-old woman with a 23 year history of Devic’s syndrome continued to have frequent attacks of optic neuritis unresponsive to daily corticosteroids and azathioprine. Since initiation of monthly IVIG 5½ years ago she has had no further definite attacks. She has also noted minimal improvement in color perception. Patient 2: A 58-year-old woman with a three year history of Devic’s syndrome experienced five attacks during the first 16 months of disease. Monthly IVIG was associated with complete cessation of relapses and significantly improved neurological status over one year of treatment. Conclusions: Because active Devic’s disease often results in severe, permanent neurological impairment, preventive intervention should be considered. These cases suggest that IVIG may be effective in preventing attacks and possibly in enhancing neurological recovery. Randomized controlled trials will be needed to confirm this and to determine optimal dosing and treatment duration.

RÉSUMÉ: Neuro-myélite optique aiguë de Devic traitée par injection intraveineuse de gamma globuline.

Introduction : Le syndrome de Devic est une maladie démyélinisante de la moelle épinière et des nerfs optiques. Il a en général un mauvais pronostic, probablement à cause de la présence de nécrose dans les lésions. Il n’existe pas de traitement dont l’efficacité ait été démontrée. Les récidives sont généralement traitées par des corticostéroïdes et les patients qui ont une maladie récidivante reçoivent un traitement immunosuppresseur à long terme. L’injection intraveineuse de gamma globuline (IVIG) et la plasmaphérèse sont des options de traitement logiques considérant le fait que le syndrome de Devic soit probablement une maladie à médiation immunitaire. Nous rapportons les cas de deux patients atteints du syndrome de Devic dont la maladie s’est stabilisée à la suite de traitements mensuels par IVGG. Observations: Une patiente de 42 ans, ayant une histoire de syndrome de Devic depuis 23 ans, présentait des attaques fréquentes de névrite optique qui ne répondaient pas à la corticothérapie quotidienne et à l’azathioprine. Depuis le début de l’IVGG il y a 5 ans et demi, elle n’a pas eu d’autre épisode typique. Elle a également noté une légère amélioration dans la perception des couleurs. Une autre femme âgée de 58 ans, ayant une histoire de syndrome de Devic depuis trois ans, a présenté cinq attaques pendant les 16 premiers mois de la maladie. Depuis l’administration mensuelle d’IVGG, elle n’a pas présenté de récidive et son état neurologique s’est amélioré de façon importante en un an de traitement. Conclusions: Une intervention préventive devrait être considérée dans les cas de maladie de Devic parce que la maladie provoque souvent une atteinte neurologique sévère et permanente. Ces cas suggèrent que l’IVGG peut être efficace dans la prévention des crises et peut favoriser la récupération neurologique. Ces observations méritent confirmation par des essais randomisés contrôlés et la posologie ainsi que la durée du traitement sont à déterminer.

**PATIENT 1**

This 43-year-old woman developed symptoms and signs of mild incomplete transverse myelitis with a progressive sensory level and a positive Lhermitte’s sign at age 19. Myelography showed an expanded cervical cord due to an intramedullary lesion. Cerebrospinal fluid was acellular but protein was moderately elevated twice (0.83 g/L, 0.61 g/L). Protein electrophoresis was normal both times. Laboratory investigation, including ANA, ENA and anti-DNA antibodies was normal. Visual and auditory evoked potentials were normal. She recovered completely.

Within two years she developed recurrent episodes of right optic neuritis leading to severe irreversible visual loss in her right eye (light perception only). Three years later she developed left optic neuritis. Over the next ten years increasingly frequent relapses of left optic neuritis occurred. Vision initially recovered well with intravenous methylprednisolone (IVMP) leaving her visual acuity in the left eye at 20/30. Fifteen years after onset, treatment of a relapse of optic neuritis was delayed until the fourth day. Vision remained severely impaired at 20/800 in the left eye. Over the next three years she had eight relapses of optic neuritis manifest as loss of remaining vision and eye pain exacerbated by eye movement. The major concern was that while she now had severe bilateral visual impairment, she was at risk for further episodes of transverse myelitis leading to further severe disability or death. Azathioprine and prednisone did not affect relapse frequency over one year.

At age 38 her brain MRI was normal and cervical spine MRI showed T2 hyperintensity within the central and posterior aspects of the cord, extending from C3 - C7, without cord expansion. Small areas of T1 and T2 prolongation, comparable to CSF, were present within the lesion. These findings were consistent with cavitating demyelination. Monthly IVIG (60g) was started and has continued for the past 5½ years except for five months during a worldwide IVIG shortage. She has remained stable with two very minor, brief episodes of possible optic neuritis occurring early during the treatment period. Both presented solely as eye pain but were treated within 24 hours with high dose oral prednisone even though her neurologist was unconvinced that these episodes represented optic neuritis. During treatment with IVIG vision in her left eye became capable of differentiating green from black although visual acuity remained 20/800. The right eye continued to have only light perception and her neurological examination otherwise remained normal. Objective assessment using evoked potentials remains impossible due to severe visual impairment.

**PATIENT 2**

A healthy 58-year-old woman originally presented with right optic neuritis in October 2000 at age 55. A residual central scotoma remained. In May 2001 she developed incomplete transverse myelitis manifest as an ascending sensory level over two days followed by spastic paraparesis. Spinal MRI showed a T2 hyperintense lesion at the level of T2-T5 with expansion of the cord and slight central enhancement consistent with transverse myelitis. Cervical and lumbar spine MRIs were normal. An MRI of the brain showed nonspecific tiny T2 hyperintense lesions in the white matter. Cerebrospinal fluid was not obtained. She was treated with IVMP and improved over five months. Over the following year she continued to have similar relapses of transverse myelitis every three months. She recovered gradually but nearly completely between each attack.

In August 2002 she had a severe attack of transverse myelitis resulting in spastic paraparesis, prominent sensory changes and loss of bladder function which required catheterization. Spinal MRI showed T2 hyperintense lesions from C2-5 and T1-11 with slight cord expansion in the upper thoracic cord (Figure). Brain MRI was unchanged. Laboratory testing including TSH, serum B12 level, ENA and urinalysis was normal. Antinuclear antibody was elevated at 1/320. Cerebrospinal fluid was not sent for protein electrophoresis and the patient declined repeat CSF examination. Intravenous methylprednisolone had no apparent effect within one month so IVIG (0.4 g/kg/day for five days) was initiated. This was followed by IVIG 1.0 g/kg/day over two consecutive days per month. Over the first year of treatment she has had no further attacks and her neurological status has improved significantly. Strength is now grade 4+ in both legs; she became capable of ambulating independently and now has only mild spasticity and mild bowel and bladder symptoms.

**DISCUSSION**

Devic originally described a monophasic illness with acute bilateral visual loss and incomplete transverse myelitis occurring within several months. Accepted diagnostic criteria have evolved to include an interval between events of years rather than months, unilateral optic neuritis, and a relapsing course. Differences in demographics, course, imaging, and CSF suggest...
that this syndrome is a unique entity\textsuperscript{1,4} rather than a type of multiple sclerosis. The frequent concurrence of a variety of autoantibodies and connective tissue disorders suggests that it is an autoimmune disorder.\textsuperscript{2} Pathology supports a humoral mechanism as being responsible for the pathogenesis of Devic’s syndrome.\textsuperscript{3} This would favor treatments commonly used for antibody mediated disorders such as IVIG or plasma exchange. Both of our patients fit current clinical criteria for Devic’s syndrome and the diagnosis is supported by normal brain MRI, spinal MRI typical for this syndrome. In the first case, the absence of oligoclonal bands, continued absence of other CNS involvement, and persistent disease activity over 22 years, supports the diagnosis of Devic’s syndrome.

The severe impairment that often occurs in Devic’s disease, and the frequent necrosis at autopsy, suggest that relapses should be treated aggressively and that preventive intervention should be considered. Relapses have been reported to respond to IVMP and, when refractory, plasma exchange has been effective.\textsuperscript{1} It is unknown, however, if any preventive intervention alters the outcome of this disease. Chronic corticosteroids with azathioprine have been reported to be associated with decreased disability and stabilization of relapses in seven newly diagnosed patients followed over 18 months.\textsuperscript{6} Our first patient responded to IVMP when initiated within three days of symptom onset but did not note fewer relapses while taking daily prednisone and azathioprine. Our second patient eventually failed to respond to acute corticosteroids for a severe relapse but IVIG was associated with clinical improvement. Monthly IVIG was associated with probable cessation of relapses in both cases.

These cases suggest that IVIG may be effective in preventing attacks and possibly in enhancing neurological recovery. Randomized controlled trials will be needed to confirm these outcomes and determine optimal dosing and treatment duration. Because both IVIG and plasma exchange are often effective in antibody mediated diseases, proving their benefit in Devic’s syndrome would argue in favor of it being antibody-mediated. Recent reports of an autoantibody specific to neuromyelitis optica support this suspicion.\textsuperscript{7}

Evaluation of the potential for IVIG to allow or stimulate recovery is also intriguing and could provide insights into mechanisms of demyelination and myelin repair. Although immunoglobulins directed against CNS components can promote oligodendroglial proliferation and promote new myelin synthesis in animal models, clinical trials of IVIG in multiple sclerosis have had contradictory outcomes. Perhaps previous trial results in multiple sclerosis are related to inclusion of multiple sclerosis patients with differing pathological subtypes as the patterns of demyelination and oligodendrocyte pathology differ among multiple sclerosis patients.\textsuperscript{9}

REFERENCES