Neuromyelitis Optica

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ABSTRACT

Neuromyelitis optica disease is characterized by simultaneous or successive attacks involving both the optics nerves and spinal cord without any evidence of the disease elsewhere. We report a 22-year-old Saudi woman with relapsing neuromyelitis optica disease. She had all the clinical, cerebrospinal fluid, and radiological features that differ from primary demyelinating disease. However, our patient responded well to long-term corticosteroid therapy and azathioprine with improvement in her expanded disability status scale, and ambulation. In addition, no acute relapses occurred with significant improvement on magnetic resonance imaging lesions and favorable outcome.

Keywords: Delvic's syndrome, multiple sclerosis, corticosteroids, immunosuppressant, prognosis.

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Neuromyelitis optica (NMO) is a rare disease. The controversy regarding the precise classification of Devic's disease among the inflammatory demyelinating diseases in general and multiple sclerosis (MS) in particular began in 1894 when Eugene' Devic and his student Gault added some patients of those with an illness characterized by acute or subacute myelopathy.[1-4] Gault proposed a separate diagnostic category for patients with NMO, a disease which later became known by Devic's name.[5] In some cases, it is considered to be a variant of MS, but some authors conclude that Devic's NMO may be a separate nosological entity with clinical, cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) features, different from classical MS.[4,5,7-10]

Case Report. A 22-year-old Saudi woman was previously healthy until 1995, when she developed sudden pain in the left eye followed by total blindness with no recovery after receiving high dose methyl prednisolone. Two months later, she developed another attack of optic neuritis involving the right eye with incomplete recovery after oral steroids. Since then, she has continued to have recurrent attacks of optic neuritis every 3-4 months. In December 1999, she was brought to accident and emergency with paresthesia and numbness over the right leg, followed a few days later by progressive ascending weakness of the 4 extremities, more on the right side. Two weeks later, she was unable to walk without assistance. She also complained of Lhermitte's symptoms, and urge incontinence. On neurological examination, she looked depressed with severe bilateral visual loss (20/800), only light perception and the pupils were dilated and not reactive to light. Fundi showed bilateral optic atrophy. She had spastic quadriparesis, a power of 2-3/5 on the right upper limb and both lower limbs, and 4/5 on the left upper limb with truncal sensory level up to D4. She had dissociated anesthesia, impaired pain and temperature sensation on the right side and impaired position sense on the left side. Her expanded disability status scale (EDSS) on

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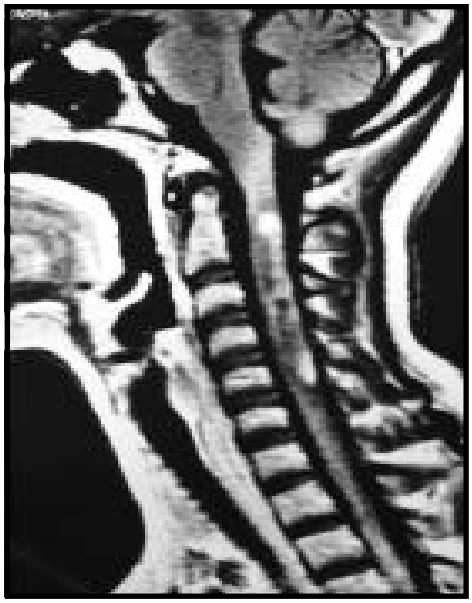

Figure 1 - MR of the spinal cord, saggital T_1 post contrast injection shows patchy nonhomogenous enhancement.

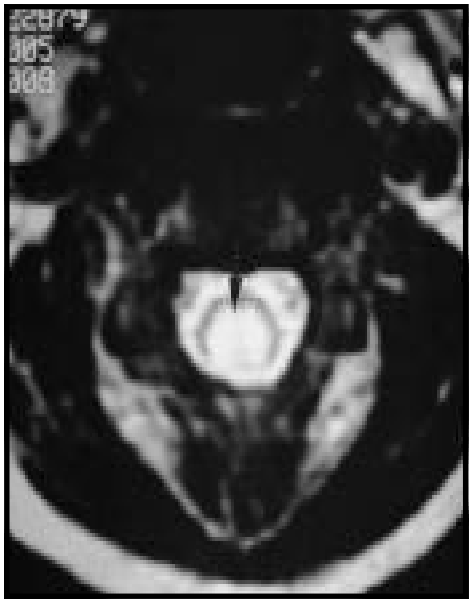

Figure 2 - MR of the spinal cord, axial T_2 of the cervical cord shows intramedullary high signal lesion involving the nearly the entire cord, with sparing of small portion anteriorly (arrow).

presentation was 6.5. An urgent MRI cervical spine (both T1 and T2 weighted sequence) was carried out to rule out cord compression. The T2-weighted images showed an intramedullary hyperintense lesion extending from C2 through C5 occupying more than 2/3 of the cord surface area with cord swelling. Patchy enhancement was demonstrated in the post-contrast images predominantly posterior. The initial brain MR study showed small foci of hyperintensities in the splenium of the corpus callosum and the centrum semiovali (**Figure 1, 2, 3**). Repeated MRI brain 9 months later did not reveal convincing evidence of an intracranial demyelinating lesion. The initial visual evoked potentials showed no reproducible potentials that could be obtained bilaterally with normal brain stem evoked potentials (BAEPs) while somatosensory evoked potential (SSEP) revealed abnormal conduction at cervical level of spinal cord on the right side. Cerebrospinal fluid carried out in the acute phase showed no cells, normal sugar, and slightly high CSF protein (0.55), but normal CSF albumin level (0.343) and serum/ CSF albumin ratio. TPHA, treponema Immunoglobulin (IgM) and FTA total CSF antibodies were all negative. Cerebrospinal fluid IgG and IgG/albumin ratio were both normal (0.05 and 0.6), no oligoclonal bands were detected. Her blood work up showed normal hematological and biochemical tests. The HLA typing was A2, A11, B50, B60, CW3, CW61 and DR10. Anticardiolipin (IgG and IgM) were within normal limits. ANCA autoimmune screen were negative. The patient received 1gm of intravenous methyl prednisolone daily for 5 days, with no improvement clinically (EDSS 6.5). Subsequently, she was started and maintained an oral prednisolone (1mg/kg/d). On the 3rd week, she was started on Azathioprine (2mg/kg/ d) and she was kept on calcium and vitamin D supplements, high protein diet, and antiacid (Ranitidine). On the 8th week; oral prednisolone was tapered slowly with complete blood count and liver function tests monitored initially weekly for one month, then monthly for 3 months, then every 3 months. She was seen every 3 months in the outpatient clinic and complete blood count and renal function were monitored. Six months later, she became cushinoid with subjective feeling of light perception on the left eye. Her motor examination showed power of 4/5 and she can walk independently for a short distance. No new or worsening of her neurological symptoms or signs were appreciated and her EDSS was 5.5. One year later, she was on prednisolone 10mg/od and azathioprine 100mg/od with much improvement regarding ambulation, she can walk for several meters (>20 meters) without assistance, but she became fatigued (EDSS was 3.5), with better sphincter control, but no change in her vision. She also complained of epigastic pain, diagnosed as gasteritis confirmed by endoscopy. At that time, MRI of the cervical spine showed no abnormal signal intensities at T1 and T2 (**Figure 4**). Repeated SSEP for both median and tibials was reported to be normal. Again, she was seen 15 months later and her motor examination of all limbs showed power of 4/5, normal sensation and gait but severe visual loss and her EDSS was 2.5. The patient

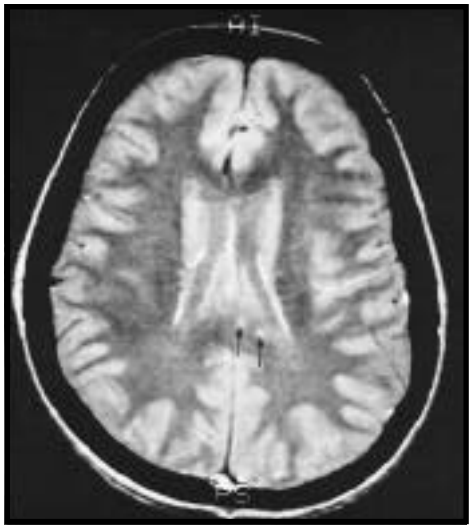

Figure 3 - Ax Proton density of the brain (TR = 5000, TE = 30). At the level of the body of the lateral ventricles showing tiny hyperintense lesions in the splenic of the corpus callosum (arrows).

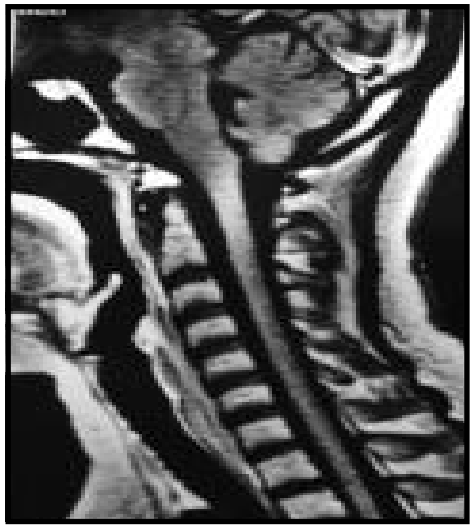

Figure 4 - Follow up Sag T_1 post contrast injection (TR = 5000, TE = 35) showed absence of enhancement in the cervical cord.

was kept on prednisolone 7.5 mg od and azathioprine 100 mg od, and is still under regular follow up.

Discussion. So, using the diagnostic criteria of Dean et al,[6] our patient fits the diagnosis of NMO, her disease started with severe neurological insult affecting optic pathway, followed by spinal cord lesion in a relapsing and remitting pattern. It was confirmed by the typical MRI appearance and results of CSF which differentiate it from MS.[6] We used long term steroid and azathioprine in our patient with regular follow up using ambulation, sphincter control, and EDSS. The patient showed great improvement regarding ambulation, sphincter control, and EDSS but not for vision. There were no new neurological symptoms or deterioration of her neurological status, but marked improvement in her EDSS. Remarkably, the signal changes seen in cervical MRI resolved completely. So did the somatosensory evoked potential, but not for visual evoked potential after being maintained on this regimen. She did not experience any serious side effects from medications except for cushinoid features and gasteritis, which improved with tapering steroids and the use of antiacids. However, spontaneous remission was reported and a multicenter, double blind placebo controlled trial of immunotherapy in NMO is required to determine the long term safety of medication and etiology of the disease. Neuromyelitis optica should be considered as a distinct clinico pathological entity different from MS, and this might explain poor response to cyclophosphamide, methotreate and interferon therapy.[7-8]

Most cases of MS are identified among Asian, African, Afrocaribbean or Mediterranean people. In contrast, MS occurs rarely in Japanese and other Asian's and is virtually unknown in tropics, where demyelinating diseases follow Devic's pattern, there are no published statistics on NMO in the United Kingdom and North Europe.[5,9] There is no evidence of hereditary influence, although Alpine in 1938 report NMO in identical twins, but he attributed it to an infectious agent.[10] Men and women are affected equally, although Stansburry in 1949 reported it to be more common in women. In both sexes, the incidence in the first 5 decades is equal, but there after it declines.[5] It affects the age group between 5 and 66 years.[5,11] It is a sporadic disease, the reason for particular susceptibility of optic nerves and spinal cords is not known.[12] The etiology is not identified, but an immunological mechanisms of tissue damage seems likely[4] and Stansburry[11] proposed various theories, which were categorized into infections such as variella, mumps, rubella, and infectious mononucleosus, however, organisms were never isolated[13,14] and its probably immunological.[9,15] Some authors reported association with pulmonary tuberculosis[16,17] and rubella vaccination.[18] Also seen with other demyelinating disease,[19] collagen vascular disorder such as systemic lupus erythematosus,[9,20] antiphospholipid, antibody syndrome, neuro-sarcoidosis, neuro-behcet's and mixed connective tissue diseases[9] or in association with organ – specific antibodies in serum and CSF.[9,15-20] Nevertheless, a significant number of cases do not have an underlying predisposing disease.

The pathological changes are mainly demyelinating plagues, and cavitation of both optic

nerve, chiasma, and spinal cord, without evidence elsewhere. These changes involve the whole cross sectioned area of both gray and white matter, and more commonly affect the cervical and upper thoracic region and may continue for many segments with necrotic tissue tapering at each end of the lesion into small areas in the posterior column. Some have reported extensive demyelination and vascular infiltration or cystic degeneration of both optic nerve and spinal cord.[21,26] These lesions appear microscopically as thin and soft with loss of demarcation between gray and white matter and sometimes necrosis. The pathogenesis of cord necrosis is thought to be due to compression, ischemia secondary to edema and cord swelling constrained a fully stretched pia in a closed spinal canal or bony foramen in the case of the optic nerves.[21-24] Microscopically, the hallmark is the numerous thickened, hyalinized blood vessels, with patchy or confluent lesions that characteristically lack a perivascular lymphocytic inflammatory infiltrate but lipid filled macrophages may sometimes be seen.[24] Mandler et al[22] postulated that lympocytic infiltrate either never happens or is due to chronicity of the lesion and its absence accounts for the lack of oligoclonal bands in CSF. These pathological changes does not differentiate NMO from schilder's myelin clastic diffuse sclerosis,[23] subacute necrotic myelopathy of Fois and AlaJounanine and progressive necrotic myelopathy.[25] In long survival, the cord appears shrunken throughout most of its length with gliosis, cavity formation, prominent mesengeal proliferation and wallerian degeneration of ascending and descending tracts may be present. The clinical manifestations of the disease were variable.[4,26] A history of flu-like illness may precede the onset of the disease in one 3rd.[5] The classic restrictive criteria of Devic's originally included the monophasic illness, with acute or subacute optic neuritis and severe acute complete transverse myelitis occurring simultaneously or within an 8 week period in a patient aged between 9 and 60 years.[1-3,9,27] The optic neuritis may start bilaterally in 40% or unilaterally with eye pain and rapidly progress to visual loss of variable severity. Both eyes can be involved within hours, days, weeks or even months with intervening periods of remission. Bilateral blindness eventually occurs in 85% of cases. Myelopathy may occur simultaneously or may precede or follow the visual symptoms. The ocular fundi are usually normal or can be slightly blurred, or may have papilledema or eventually optic atrophy. Other ocular manifestations are central scotoma, generalized constriction of field, bitemporal hemanopia, color blindness or total blindness. Ophthalmoplegia was reported in some cases (Stansburry 1949), transient ptosis, Horner's, decreased conjugate movement and nystagmus all were described. The pupils are normal except for dilatation corresponding to the degree of visual loss, with sluggish or absent light reflex. The cardinal features of myelopathy are those of acute, complete, transverse cord lesion causing severe paraparesis or quadriparesis with or without sensory involvement and sphincteric dysfunction evolves over one day to 2 weeks.[5]

The growing literature provided cases with evidence[9,24] of unilateral optic nerve involvement or partial cord lesions. Multiphasic illness sometimes with a clinical presentation of MS type pattern,[19] and expanding interval between the 2 classical manifestations of the syndrome as long as 2.5 years with a wide age range of sufferers and probably more demyelination in the brain MRI or autopsy. Also, some cases with infectious or immunological etiological links are associated with NMO.[8,14,16,17] Dean et al[6] reviewed 71 patients with NMO, in the Mayo clinic and proposed a diagnostic criteria which includes 1. Absolute criteria and 2. One major supportive criteria or 2 minor supportive criteria. The absolute criteria includes 1. Acute optic neuritis, 2. Acute myelitis, and 3. No evidence of clinical disease outside the optic nerve or spinal cord. The major supportive criteria includes 1. Negative brain MRI at onset (does not meet criteria of Paty et al),[11,27,33] 2. Spinal cord MRI with signal abnormality extending over >3 vertebral segments and 3. Cerebro-spinal fluid phocytosis of >50 white blood cell/mm^3 or > 5 neutrophils/mm^3. While the minor supportive critria are those of 1. Bilateral optic neuritis, 2. Severe optic neuritis with fixed visual activity worse than 20/20 in at least one eye and 3. Severe fixed, attack related weakness (MRC grade <2) in one or more limb.

The diagnosis should be made by using clinical evolution, imaging and CSF, although the firm diagnosis can only be made by autopsy.[28] Cerebrospinal abnormalities during acute phase are mainly polymorph pleocytosis (50-100 cell/mm^3), although lymphocytic pleocytosis can be detected at disease onset and fluctuates with the disease activity. In some reports, the cell count is as high as 3000 cells (Popow).[5] Oligoclonal bands IgG is absent, but can be detected transiently in some cases during the onset of the illness.[22] An elevated IgG index may be seen, and this is attributed to the break down of blood brain barriers (BBB) rather than intrathecal production. The CSF albumin is high and serum/ CSF albumin ratios is low (due to leakage of BBB).[22] The CSF sugar may be as low as 1.7mg/dL.[5] The treponemia immobilization test (TPI) and venereal disease research laboratory test (VDRL) are usually negative. The spinal, T2-weighted images show the lesion with spinal characteristics; it tends to involve usually multiple segments (>3 vertebrae), with diffuse swelling of both gray and white matter, which are shown as high signal intensity.

In T1-weighted, it appears as hypointense due to necrosis and cavitation, all these features do not occur in MS.[29,30] Mandler et al[22] and other previous studies have emphasized the lack of involvement of the brain; however, clinically silent white matter abnormalities are seen in a proportion of patients, which raises the possibility of MS.[22,29,30] Also, O'Riordan et al[9] have the same observations, but these lesions lack the characteristic periventricular distribution on serial MRI scans.

Initial MRI should be carried out to rule out intramedullary tumor, arteriovenous malformation, infection, trauma, and other conditions, such as progressive necrotic myelopathy, subacute necrotic myelopathy and shilder's disease, in some cases MRI may be normal initially, which leads to a serious problem in diagnosis and may be solved by repeat MRI.[23,25,28,31]

Management. High dose steroids is the treatment of choice. Phalke and Shrivastava[5] described a cure after use of cortisone, however; spontaneous remission cannot be ruled out. Some reports showed that long term steroids and azathioprine have significant results with improvement in EDSS and no relapses.[7] Steroids, plasma exchange and a variety of immunosuppressive agents can modulate the natural history of the disease but with no lasting benefit in most instances.[5,9,30,32,33] Patients with idiopathic NMO or in association with connective tissue disease have poor prognosis and high mortality.[34] Rilling et al[34] and Bonnet et al[35] used cyclophosphomide in relapsing form of NMO in association with systemic lupus erythematosus and steroid or plasmapharesis for acute disseminated encephalomyelitis. Those left with disability require nursing care and other measures to prevent decubiti and secondary infections.[5] Neuromyelitis optica carries a poor prognosis, with overall mortality between 35%-50%. Twenty percent die during the acute stage due to the destructive nature of the disease and rapidly fulminant course, while 30% die as a result of complications after many months and the remaining 50% survive with variable degrees of disability, however, spontaneous complete recovery was reported.[5,16] In those who survive, vision may fully return without recovery of spinal cord lesion or may remain defective with or without residual effect of spinal cord lesions. In patients with optic atrophy, light perception usually returns, but the visual acuity is remarkably impaired considering the severity of optic atrophy. Those with cervical myelopathy are at risk of respiratory failure[36] and the end stage of NMO may not be reached for many months or years.

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