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"A clinical case report where clinical neurophysiology helped the diagnosis and management of the patient"

Clinical neurophysiology and the Japanese woman with hiccups and bilateral lower limb weakness

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The case presented here is of a patient who was under the care of the Neurology department of a University hospital in Tokyo during my medical elective in Japan. I am very grateful to everyone concerned for granting me permission to publish the clinical details for educational purposes. Some details have been changed slightly to maintain patient anonymity.

Introduction

"Swiftly", wrote Sir Charles Sherrington in *Man on His Nature*, "the head mass becomes an enchanted loom where millions of flashing shuttles weave a dissolving pattern...a shifting harmony of subpatterns". This most eloquent of passages from the pre-eminent neurophysiologist represents a timeless tribute to the mystifying complexities and delicate intricacies of our brain and, by extension, our entire nervous system. Our understanding of how this elusive entity functions in health – and how it malfunctions in disease – has progressed in leaps and bounds in the bygone century, due in no small part to advances in accurately and sensitively measuring the electrical basis of neural function. This has allowed the discipline of clinical neurophysiology, concerned with the qualitative and quantitative assessment of neuromuscular electrical 'signals' in relation to various structural and functional pathologies, to flourish and establish itself as an important player in the investigation and management of many neurosurgical and even psychiatric conditions. This essay illustrates how clinical neurophysiology, by offering an essentially non-invasive window into the operations of the "enchanted loom", provided essential ancillary support in the evaluation of a patient with clinical features and an eventual diagnosis of great interest.

Case report

A 59 year-old Japanese woman was initially seen by her family physician following a two month history of increasingly prolonging bouts of hiccups, which tended to occur several times every day

and lasted for 30-60 minutes each day, occasionally being accompanied by mild nausea. She did not note any specific relieving or exacerbating factors and denied the presence of any other gastrointestinal symptoms. She had no other systemic or neurological complaints at that point. Her past medical history was significant for rheumatoid factor-negative rheumatoid arthritis which was diagnosed five years earlier and was well controlled by penicillamine. Other aspects of her history and her general examination were unremarkable. Her family doctor initiated symptomatic treatment with chlorpromazine and she noticed a significant improvement in her condition after one week.

Shortly afterwards, however, she experienced numerous fleeting episodes of bilateral lower limb weakness and hypoesthesia over a period of several weeks. She denied any other neurological symptoms, back pain, bowel or bladder problems at that point and arranged a self-referral to a neurologist in a different city for evaluation. The neurological examination in that instance was normal except for mildly reduced muscle strength (grade 4/5 weakness) in her left leg. It is believed that a provisional diagnosis of spinal stenosis was reached some time later on the basis of spinal magnetic resonance imaging (MRI) findings (the images were unfortunately unavailable to us); she declined any follow-up appointments as her symptoms had resolved completely by that time.

Although still asymptomatic, she presented several months later to our hospital requesting a general neurosurgical review in view of her provisional diagnosis. At this point, neurological examination revealed mild, diffuse, bilateral visual field loss on confrontation testing, which was later confirmed with formal visual field testing. There were no pupillary abnormalities and visual acuity, colour vision and fundoscopic examination were noted as being normal. Full-field pattern-reversal visual evoked potential (VEP) testing was performed using monocular stimulation with high contrast black and white checkerboards (1-3 reversals/second) and showed reduced P100 wave amplitude (5.76 and 5.45 µV for the right and left, respectively) with normal latency in both eyes. Laboratory analysis at this stage revealed only a mild microcytic, hypochromic anaemia (haemoglobin of 10.8 g/dL), with normal biochemistry, negative antinuclear, anti-aquaporin-4 (anti-AQP4), anti-Ro/SSA and anti-La/SSB antibodies, a normal erythrocyte sedimentation rate and normal angiotensin-converting enzyme levels. Cerebrospinal fluid (CSF) analysis showed a mild pleocytosis (16 cells/ml, predominantly lymphocytes), normal protein and biochemistry, absent oligoclonal IgG bands and a normal IgG index. Brain and orbit MRI scans were carried out but did not show any suspicious or demyelinating lesions, nor was there any swelling or enhancement of the optic chiasm and the optic nerves. An MRI scan of her spine was arranged together with another appointment with a neurosurgeon; however, owing to her other commitments, she was forced to postpone these for several weeks.

One week before her appointment, she developed bilateral lower limb weakness and paraesthesia which progressed over a period of a few days, without any other symptoms. This then increased in severity over two days and was then accompanied by urinary incontinence; at this

point, she became unable to walk and presented to our hospital. On examination, tone in her lower limbs was normal but there was markedly and equally reduced strength on both sides (grade 2/5), hyperactive deep tendon reflexes, extensor plantar responses and absent sensation to all modalities below the T6/T7 level. The neurological status of her upper extremities and cranial nerves was normal, apart from the aforementioned bilateral visual field defect. An MRI scan of her spine showed high signal intensities on T2-weighted images in the T1-T3 and T9-11 segments, with entire cross-section involvement and no gadolinium enhancement (Figure 1A, 1B). The findings from laboratory and CSF evaluation were unchanged, with the important exception of elevated CSF L-lactate levels and, especially in light of her previous VEP results, the detection of high titres of anti-AQP4 antibodies in both CSF and serum (level 1:1000). Furthermore, negative results were obtained for the lupus erythematosus cell test and when testing for serum anti-neutrophil cytoplasmic antibodies. Blood tests for hepatitis B, C, syphilis and HIV were also negative.

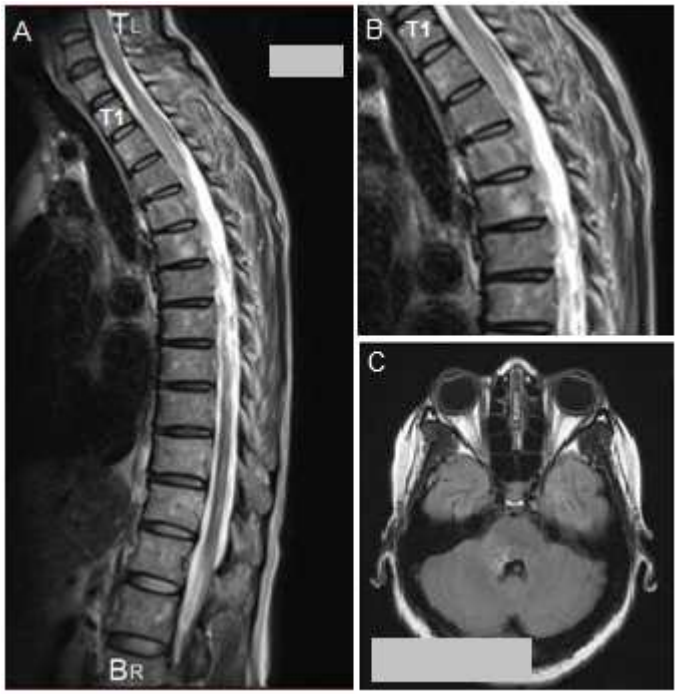

Figure 1: (A) Spinal cord T-2 weighted MRI in the sagittal plane showing cord thickening and intraparenchymal hyperintensities spanning multiple thoracic segments. (B) Close up of upper thoracic cord. (C) Brain MRI in the transverse plane showing some enhancement around the fourth ventricle.

These findings, taken *in toto*, were highly suggestive of a diagnosis of neuromyelitis optica (NMO)/NMO spectrum disorder (NMOSD) and she was treated with high-dose (1000 mg/day) intravenous methylprednisolone for three days for her acute myelitis. This failed to instigate a substantial clinical improvement and she received therapeutic plasma exchange over two weeks (four exchanges every other day adjusted according to response; 2-3 L each). This yielded a much

more potent 'rescue' effect with a return to near-normal sensation and decreased lower limb weakness (grade 4/5 bilaterally), which in turn mirrored the return in her ability to ambulate, albeit with the help of a walking aid, and her general functional improvement. Regular ophthalmic assessments, including VEPs, were performed during this two-week period but they did not show any new problems. Long-term oral immunosuppressive treatment with azathioprine (2.5 mg/kg/day) was initiated at the end of the two weeks, being initially combined with prednisolone cover (20 mg/day). Interestingly, a brain MRI scan carried out at her initial presentation was reported as showing several very small white matter lesions and two discrete linear lesions affecting the solitary nucleus (Figure 1C). On further questioning, it was discovered that our patient had experienced a relapse of her troublesome hiccups and nausea in the days and weeks preceding her latest presentation. After undergoing a gastroscopy at a different facility, she was diagnosed with mild erosive gastritis (possibly secondary to long-term non-steroidal anti-inflammatory drug use for her rheumatoid arthritis) and gastro-oesophageal reflux disease, and her hiccups and nausea improved following medical therapy.

Her recovery from this acute event continued uneventfully for many months and repeat MRI scans of the brain and spinal cord did not disclose any new or expanding lesions after nine months of azathioprine therapy. Serum titre of anti-AQP4 antibodies was 1:250 during remission. However, she still endured considerable disability stemming from mildly reduced lower limb sensation – but no pain – and weakness bilaterally, impairing her ability to walk unaided and corresponding to an expanded disability status scale (EDSS) score[1] of 5.5. Over the next few months, her condition steadily deteriorated to the point where she required hospital admission for further investigation and management. Her examination at this stage revealed lower limb weakness bilaterally (grade 3/5), areflexia of knee and ankle jerks on both sides and unobtainable plantar responses. No muscle fasciculations or atrophic changes were observed. Sensation to all modalities was reduced or absent in both lower limbs and a definite stocking pattern was discernible (extending to just below the knees). She denied any bowel or bladder dysfunction. Nerve conduction studies were performed, with the electrophysiological variables being regarded as abnormal if they were more than 2 standard deviations from the means of healthy age-matched controls at our facility. Motor and sensory nerve conduction studies were completely normal for the median and ulnar nerves, stimulated up to the axilla, on both sides. However, for both tibial nerves, conduction velocity was slowed, there was prolongation of distal motor and F-wave latencies (see Figure 2), and dispersion and distance-dependent reduction of the compound motor action potential (CMAP) amplitude. The sural nerve sensory nerve action potential (SNAP) conduction velocity was reduced bilaterally and the distal sensory latency was prolonged, with low amplitude responses being recorded. Laboratory studies, including glycated haemoglobin and thyroid function tests, and tests for several anti-

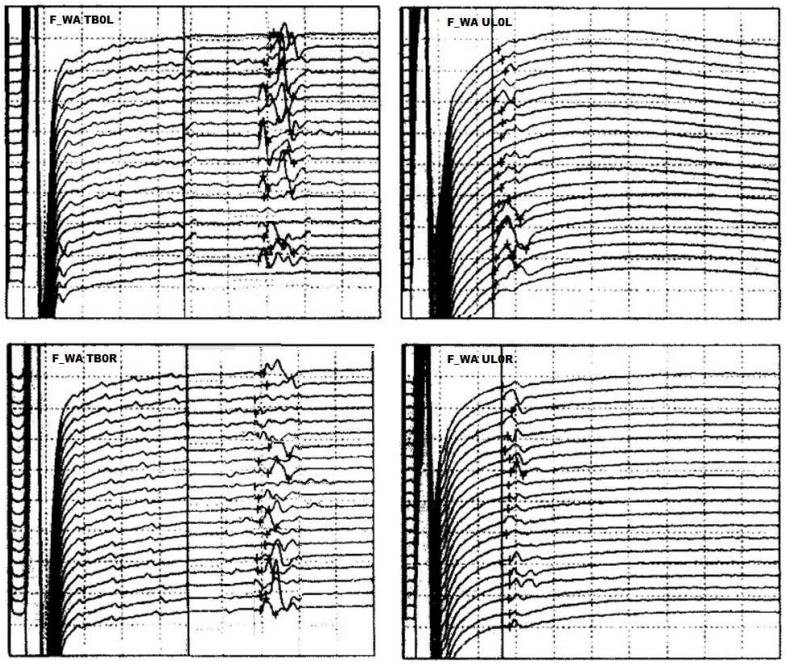

Figure 2: F-wave studies showing prolonged and somewhat variable F-wave latencies for both tibial nerves (left); normal responses from the ulnar nerves shown on the right.

neuronal antibodies, including anti-ganglioside and anti-glycolipid antibodies, were negative. Serum anti-AQP4 antibody titre was raised at 1:1000. A concomitant diagnosis of Sjogren's syndrome (and related peripheral neuropathy) was briefly entertained but she did not have any ocular or oral symptoms, and had already tested negative for the most typical autoantibodies. Our patient had then expressed a desire to defer further investigations (including imaging of the spine and nerve roots) until a later date. In the interim, a treatment plan involving regular plasma exchanges and increased azathioprine dosing (3 mg/kg/day) was formulated to ameliorate the possible demyelinating lower limb peripheral neuropathy – believed to be related to her underlying NMO – suggested by the abnormal nerve conduction findings. Pyridoxine supplementation was also instituted given our patient's long history of penicillamine intake and a rheumatology referral was made as some concern was raised about the risk-benefit ratio of combined azathioprine and penicillamine exposure. At the time of writing, three weeks on, the steady decline in the neurological function of her lower limbs had been arrested and, with regular physiotherapy, her overall condition had improved marginally, enabling ambulation with only limited use of walking aids.

Case discussion

NMO is a severe, immune-mediated chronic inflammatory disorder which predominantly affects the spinal cord and optic nerves. It is also known as Devic's syndrome, after Dr Eugene Devic, who described numerous cases of it in 1894, and for a long time since then it was considered to be a rare variant of multiple sclerosis (MS). It is now known, however, that the pathophysiology of NMO

is distinctly different from that of MS, with NMO being histologically characterised by astrocytic damage, axonal loss, necrosis and some demyelination[2]. Still, given that the hallmark of the disease is a relapsing-remitting optic neuritis (usually simultaneously bilateral) and longitudinally extensive transverse myelitis, atypical or unusual presentations often lead to a misdiagnosis of MS. An important distinguishing feature is the presence in NMO of a circulating IgG auto-antibody (anti-AQP4) directed against the water channel protein aquaporin-4, which is strongly expressed in astrocytes in the central nervous system. Seropositivity for this antibody has a sensitivity and specificity of 73% and 91%, respectively, and is incorporated within the conventional NMO diagnostic criteria (Table 1)[3]. NMOSD is an entity characterised by anti-AQP4 seropositivity but limited manifestations of NMO (e.g. myelitis without optic neuritis), although in many cases conversion to frank NMO occurs over time[4]. NMO is notably more common in women than men (9:1 ratio), with a median age of onset of 39 years, and is relatively rare in the Western world (prevalence ranging from 1 to 4.4/100,000)[5]. Although still uncommon, NMO is much more prevalent in Asian countries and in Japan it constitutes one-third of all demyelinating disorders[6].

For definite NMO, both of:
Optic neuritis
Myelitis
Plus two of three additional supportive criteria:
Contiguous spinal cord MRI lesion extending over ≥ 3 vertebral segments
Brain MRI not meeting Paty's diagnostic criteria for multiple sclerosis
Anti-AQP4 seropositive status

Table 1: The revised diagnostic criteria for NMO (Wingerchuk, *et al.* 2006)[7]

NMO can often be a debilitating disease and so reaching the right diagnosis quickly is imperative in order to halt the rapid accrual of neurological deficits. However, as the case of our patient illustrates, the process of diagnosing and treating it can be plagued with ambiguity. For instance, our patient's initial neurological symptoms evolved gradually and in a non-specific pattern, and the serendipitous discovery of her slight (and unbeknown to her) visual field defect was the first indication of more widespread neurological pathology. At this stage, VEP testing assumed a central role in her evaluation as the other ophthalmic assessments failed to clarify the nature of the defect. VEPs can sensitively detect abnormal neural transmission within the visual pathway (from the retina to the striate cortex) and their use is recommended by experts from the NMO Study Group as part of a minimum electrophysiological dataset, which also includes median and tibial somatosensory and motor evoked potentials[8]. The P100 latency for our patient was normal but had a reduced amplitude, a finding which is concordant with the typical NMO pattern proposed by several case reports and studies[9,10]. For example, in a study of 19 patients meeting the criteria for the diagnosis of definite NMO, no VEP responses were detected in 18 (out of 38) eyes, while reduced P100 wave amplitudes with normal latencies were found in 65% of the remaining 20 eyes; only 5 eyes showed

normal responses[11]. This pattern is readily distinguishable from that resulting from widely disseminated demyelination, as in MS, where there is characteristically prolonged P100 latencies with normal amplitudes, with latencies increasing with disease progression[12,13]. Interestingly, no significant correlations were found between the severity of visual dysfunction (based on visual acuity assessment) and the different electrophysiological parameters, implying that abnormal VEP results can potentially be the first and only abnormality detected in patients with subclinical NMO optic neuritis.

Differentiating between MS and NMO in these situations is complicated further by the fact that, especially in Asian populations, MS is frequently characterised by the selective and severe involvement of the optic nerves and spinal cord (termed opticospinal MS). Whether this is the same entity as NMO has been the subject of some nosological controversy, particularly as the majority of patients with opticospinal MS test positive for anti-AQP4 antibodies[14]. VEP testing can again be of utility here, as demonstrated by a study of 111 Japanese patients with either suspected relapsing-remitting/relapsing-progressive MS or opticospinal MS, which showed that reduced amplitude or the complete absence of the P100 component was more common in patients who displayed anti-AQP4 antibody positivity. Furthermore, unevoked potentials in anti-AQP4 antibody positive patients correlated with higher frequencies of MRI optic nerve and spinal cord lesions[15]. It is known that these antibodies are intimately involved in propagating the vasogenic oedema which is a feature of the CNS lesions in NMO. With the optic nerve, however, oedematous distension is spatially limited by the orbital cavity, thereby promoting vascular compromise and the secondary ischaemic necrosis which is indicated by the VEP findings[16,17]. Still, despite the plausibility of the proposed mechanisms, the definitions of characteristic VEP 'NMO patterns' remain far from unequivocal. For instance, a more recent study of 43 NMO patients found a heterogeneous cluster of patterns, including prolonged latencies (indicating demyelination) in the majority patients[18], however, this should be considered alongside the caveat that the study was solely a retrospective analysis and had several technical limitations (e.g. lack of other ophthalmic assessments).

A unique and rather fortunate aspect of this case is that our patient had not yet developed any notable visual symptoms. Another interesting (but perhaps coincidental) feature relates to her recurrent hiccups and the location of some of the lesions detected on her brain MRI scans. It is well appreciated that lesions of the medulla involving the area postrema and solitary nucleus can give rise to symptoms such as intractable hiccups, nausea and vomiting in NMO (indeed, they can be the initial and sole manifestation)[19,20]. More interesting still, however, is the nature of the peripheral neuropathy she developed, as delineated by nerve conduction studies. Peripheral nervous system demyelination is a little-known complication of NMO/NMOSD, with only a few case reports and series on the topic, and is believed to be mediated by as-yet-undetermined humoral factors as opposed to anti-AQP4 antibodies (because aquaporin-4 channels are only expressed at the

astrocyte foot processes)[21]. In our patient's case, decreased distal CMAPs and SNAPs together with the reduction (less than 70% normal) of the tibial and sural nerve conduction velocities, and increased temporal dispersion and F-wave latencies, pointed to the presence of an acquired demyelinating neuropathy affecting only the lower limbs. The negative laboratory studies and lack of other clinical features excluded any secondary causes (diabetes mellitus, Sjogren's syndrome, hepatitis C, etc) of the neuropathy. In fact, it can be argued that the nerve conduction study results rendered these investigations superfluous, since the unusual distribution of the neuropathy made any secondary causes (or an inflammatory polyradiculoneuropathy unrelated to NMO) very unlikely in the first place. This distribution has been reported only once before by Aimoto, *et al.*, with their study describing similar electrophysiologic findings and a sural nerve biopsy showing patchy demyelination and segmental remyelination[22]. It is probable that there are distinctly different mechanisms contributing to the demyelination in the central and peripheral nervous systems. This is because our patient's sensory and motor disturbances improved significantly when optimal therapy was started, and her peripheral neuropathy (mechanism being unresponsive to existing treatment) and consequent neurological deficits worsened gradually over several months rather than in the sudden 'attacks' which are characteristic of NMO.

Conclusion

Given the complex and heterogeneous nature of most neurological conditions, neurology is perhaps *the* quintessential specialty heavily reliant on the close relationship between the three chief domains of clinical medicine: history and examination, anatomical assessment (e.g. imaging) and functional evaluation. Occupying the latter domain, as demonstrated by the case of NMO presented here, the use of clinical neurophysiology in conjunction with clinical acumen and the selective utilisation of other investigations was crucial in achieving a pleasing outcome for our patient. The atypical presentation of this rare disease required information to be gleaned from VEPs to help determine the diagnosis and monitor our patient's vision. The current criteria for diagnosing NMO does not explicitly warrant any particular VEP results, although determining the characteristic evoked responses in NMO and their predictive values is an important objective which may give more weighting to VEP findings. Similarly, the nerve conduction studies were central in clarifying the nature of an important complication and ruling out any other CNS or secondary causes, in turn helping to fine-tune the management of our patient (e.g. pyridoxine therapy in light of the potential contribution of penicillamine exposure to her neuropathy)[23].

Word count: 3000 words (excluding references, tables, figures and citation numbers)

References

[1] Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983; 33(11): 1444-1452.

[2] Matiello M, Jacob A, Wingerchuk DM, Weinshenker BG. Neuromyelitis optica. *Curr Opin Neurol*. 2007; 20(3): 255-260.

[3] Lennon VA1, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet*. 2004; 364(9451): 2106-2112.

[4] Lana-Peixoto MA. Devic's neuromyelitis optica: a critical review. *Arq Neuropsiquiatr*. 2008; 66(1): 120-138.

[5] Asgari N, Lillevang ST, Skejoe HP, Falah M, Stenager E, Kyvik KO. A population-based study of neuromyelitis optica in Caucasians. *Neurology*. 2011; 76(18): 1589-1595.

[6] Uzawa A, Mori M, Kuwabara S. Neuromyelitis optica: concept, immunology and treatment. *J Clin Neurosci*. 2014; 21(1): 12-21.

[7] Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology*. 2006; 66(10): 1485-1489.

[8] Trebst C, Jarius S, Berthele A, Paul F, Schippling S, Wildemann B, et al. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). *J Neurol*. 2014; 261(1): 1-16.

[9] Langwińska-Wośko E, Szulborski K, Broniek-Kowalik K. Visual evoked potentials in early diagnosis of demyelinating diseases--a case report of Devic's disease. *Med Sci Monit*. 2012; 18(10): 82-84.

[10] Yan F, Li J, Wang ZC, Liu SB, Zhang XJ. MRI findings and correlative study of MRI and visual evoked potentials in optic neuritis. Chinese J Radiol. 2008; 42(5): 484-488.

[11] Neto SP, Alvarenga RM, Vasconcelos CC, Alvarenga MP, Pinto LC, Pinto VL. Evaluation of pattern-reversal visual evoked potential in patients with neuromyelitis optica. *Mult Scler*. 2013; 19(2): 173-178.

[12] Halliday AM, McDonald WI, Mushin J. Visual evoked response in diagnosis of multiple sclerosis. *Br Med J*. 1973; 4(5893): 661-664.

[13] Walsh JC, Garrick R, Cameron J, McLeod JG. Evoked potential changes in clinically definite multiple sclerosis: a two year follow up study. *J Neurol Neurosurg Psychiatry*. 1982; 45(6): 494-500.

[14] Weinshenker BG, Wingerchuk DM, Nakashima I, Fujihara K, Lennon VA. OSMS is NMO, but not MS: proven clinically and pathologically. *Lancet Neurol*. 2006; 5(2): 110-111.

[15] Watanabe A, Matsushita T, Doi H, Matsuoka T, Shigeto H, Isobe N, et al. Multimodality-evoked potential study of anti-aquaporin-4 antibody-positive and -negative multiple sclerosis patients. *J Neurol Sci*. 2009; 281(1-2): 34-40.

[16] Hinson SR, Pittock SJ, Lucchinetti CF, Roemer SF, Fryer JP, Kryzer TJ, et al. Pathogenic potential of IgG binding to water channel extracellular domain in neuromyelitis optica. *Neurology*. 2007; 69(24): 2221-2231.

[17] Jayaraman M, Gandhi RA, Ravi P, Sen P. Multifocal visual evoked potential in optic neuritis, ischemic optic neuropathy and compressive optic neuropathy. *Indian J Ophthalmol*. 2014; 62(3): 299-304.

[18] Ringelstein M, Kleiter I, Ayzenberg I, Borisow N, Paul F, Ruprecht K, et al. Visual evoked potentials in neuromyelitis optica and its spectrum disorders. *Mult Scler*. 2014; 20(5): 617-620.

[19] Kulkarni, Kallollimath P, Subasree R, Veerendrakumar M. Intractable vomiting and hiccups as the presenting symptom of neuromyelitis optica. *Ann Indian Acad Neurol*. 2014; 17(1): 117-119.

[20] Enweluzo C, Yarra P. Neuromyelitis Optica: An Often Forgotten Cause of Intractable Nausea and Vomiting. *Case Rep Gastroenterol*. 2013; 7(2): 281-286.

[21] Warabi Y, Yamazaki M, Shimizu T, Nagao M. Abnormal nerve conduction study findings indicating the existence of peripheral neuropathy in multiple sclerosis and neuromyelitis optica. *Biomed Res Int*. 2013; 847670.

[22] Aimoto Y, Ito K, Moriwaka F, Tashiro K, Abe K. Demyelinating peripheral neuropathy in Devic disease. *Jpn J Psychiatry Neurol*. 1991; 45(4): 861-864.

[23] Pool KD, Feit H, Kirkpatrick J. Penicillamine-induced neuropathy in rheumatoid arthritis. *Ann Intern Med*. 1981; 95(4): 457-458.