

Neuromyotonia: Clinical profile of twenty cases from northwest India

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Objectives: We are presenting 20 cases of the intriguing clinico-electromyographic entity, now considered a potassium channel disorder, Neuromyotonia. Our experience with the clinical manifestations, underlying abnormalities and response to various therapies is documented. **Materials and Methods:** Patients with diffuse pain or undulating muscle movements, with or without stiffness were sent for electromyographic and further studies. Patients with “neuromyotonic discharges” were included after exclusion of hypocalcaemia. **Results:** Our cases included 19 males and one female of age group 15 to 52 years, the majority being between 30 to 45 years. Undulating movements were seen in 19, of which two had focal twitching. Muscle stiffness was a complaint in five; pain was the chief presenting complaint of 19, which started in the calf in all. Irritability, insomnia and a peculiar worried pinched face were present in 12 patients. CSF was abnormal with mildly raised protein in eight. Curiously, 11 of these patients had taken ayurvedic treatment for various complaints in the preceding one month. Bell's palsy was associated in four, peripheral neuropathy in two and residual poliomyelitis in two. Electromyographic evidence of spontaneous activity in the form of “neuromyotonic discharges” was seen in all. Antibodies to voltage gated potassium channels was tested in one patient and was positive (titer was 1028 pM). Membrane stabilizers (e.g., phenytoin sodium) in our experience did not provide adequate rapid relief; we tried high-dose intravenous Methylprednisolone in 19 with significant amelioration of complaints. One patient was offered intravenous immunoglobulin, to which he responded. **Conclusions:** Neuromyotonia is a heterogeneous condition and can present in varied ways including diffuse nonspecific pain. This uncommon condition is potentially treatable and can be picked up with high index of suspicion.

Key words: Neuromyotonia, motor unit hyperactivity, potassium channel disorders

Neuromyotonia, with all its synonyms is an enigmatic entity, in part because of its remarkable clinical pleomorphism, uncertain natural history and anecdotal response to various therapies. The term ‘Neuromyotonia’ found its place in the early papers of Zondek^[1] and Brown,^[2] but it was Isaacs^[3] who described the condition in detail. The entity manifests with varying combinations of diffuse pain, undulating twitching and muscle stiffness. Central features with behavioral changes like anxiety, restlessness, hallucinations and sleep disturbances have been reported.^[4] Electromyography documents continuous spontaneous activity in the form of discharges in doublets, triplets or multiplets with high intraburst frequency now known as “neuromyotonic discharges”.^[5]

We are documenting here 20 cases of neuromyotonia with classical electromyographic picture and their follow-up with response to various therapies. This forms the largest series of such cases from this part of the world to the best of our knowledge.

Materials and Methods

Patients were selected from the Neurology outpatient service of this large super specialty centre of northwest India over a period of three years. Patients presenting with features to suggest diffuse pain or undulating muscle twitching with or without stiffness were sent for electromyographic (EMG) studies.

EMG studies for all patients were done by two trained neurologists, on one of two machines in the Department, Nicolet or Dantec. Twenty-one patients had spontaneous discharges consistent with AAEM nomenclature for “neuromyotonic discharges”. The patients underwent further routine biochemical evaluation including serum calcium, creatine kinase and T3, T4, TSH. One patient had to be excluded as he was found to have tetany related to hypocalcaemia.

The remaining 20 patients were admitted. Clinical manifestations were noted and undulating movements recorded by videography. Associated conditions and previous treatment details were recorded. Routine blood investigation,

ultrasonography of whole abdomen, chest X-ray, CT scan chest and vasculitis screen were obtained in all patients. Cerebrospinal fluid (CSF) routine studies were done in all. CSF of ten patients was studied for oligoclonal bands. Serum antibodies to GM1 ganglioside were obtained in four and serum antibodies to voltage gated potassium channels (VGKC) could be obtained in one.

All patients were offered phenytoin at dose of 100 mg three times for initial 14 days. Then they were given choice of Methylprednisolone versus intravenous immunoglobulin. Methylprednisolone was given at 1 gm daily over four hours in 500 ml of normal saline for five days in 19 patients. One patient was given 400 mg/kg/day of intravenous immunoglobulin for five days. All patients underwent review EMG at two weeks, six weeks and then six months of completion of immune therapy.

Results

The 20 patients who were included were of the age group 15 to 52 years. Table 1 depicts the demographic profile of the patient cohort.

The clinical manifestations in our patients were pleomorphic.

- Pain was the chief presenting complaint in 19 out of 20 patients. Pain started in the calf in all of these patients, then thigh and broadly followed an ascending pattern of progression. Severity was also more in the lower limbs. Pain had some similar characteristics in all the patients, with constant aches, associated with a burning sensation, occasional feeling of crawling insects and feeling of internal bursts.
- Undulating movements were observed in 19 out of 20 patients at some point of the illness. The patient who did not have undulating movement had EMG evidence of neuromyotonic discharges. Focal twitching was seen in two patients. One was localized to the forearm and hand and the other was localized to the calf. The movement persisted during sleep.
- Muscle stiffness was a complaint in five out of 20 patients. There were no specific changes in the deep tendon reflex or superficial reflexes. Deep tendon reflexes were diminished in eight, normal in 10 and brisk in two. Plantar response was flexor in all.
- Irritability, sleep disorders, restlessness and a peculiar worried and pinched face were noticed in 12 of the 20 cases. Of these two were more severe including hallucinations, but troublesome nightmare was not noted in any patient.
- Signs of increased basal metabolic rate in the form of perspiration, tachycardia and raised temperature were seen in 16 cases.

Table 1: Demographic profile of the cases

Age group	15 to 52 years, majority between 30 to 45 years
Male: Female	19: 1
Occupation	Industrialist: 1; Teachers: 2; Private company office: 6; Drivers: 2; Farmers: 6; Daily wage laborers: 3

The duration of illness prior to presentation ranged from four weeks to eight months. Median was eight weeks.

CSF was normal in 11 patients and abnormal with mildly raised protein without pleocytosis in eight patients. Lymphocytic pleocytosis was seen in one patient with peripheral neuropathy. Oligoclonal bands were positive in the CSF of six out of ten patients.

Curiously 11 of 20 patients had been taking ayurvedic drugs for various complaints for variable period before developing diffuse pain and twitching.

Antibodies to VGKC could be obtained in one patient, which was positive (titer: 1028 pM). GM1 ganglioside antibody titres were raised in three out of four patients.

Associations with underlying/preceding neurological conditions were as in Table 2.

The electrophysiological findings were characteristic of neuromyotonic discharges. This spontaneous activity was seen in some muscles of all of our patients (20 out of 20), as it was a criterion for inclusion. There were grouped repetitive discharges in the form of doublets, triplets, multiplets with high intraburst frequency (150-300 Hz). The neuromyotonic discharges differed from myokymic discharges by high intraburst frequency, longer burst duration and waning nature of the amplitude of spontaneous discharges.

Subjective relief was inadequate at the end of two weeks of membrane-stabilizing therapy (phenytoin sodium, 100 mg tds) in all patients. The clinical response to methylprednisolone (MPS) was reported to be significant by all 19 patients; infrequent pain and fasciculations in lesser severity were the residual complaints. EMG recordings were obtained two weeks after completion of the immune therapy. The intraburst frequency and duration of spontaneous burst diminished in the majority. In four patients, occasional fasciculation potentials were observed. The patient who received intravenous immunoglobulin also reported good relief, documented on follow-up EMG.

The patients were discharged on carbamazepine maintenance. EMG recordings at six months showed absence of spontaneous activity in eight patients who were tapered off therapy in the subsequent three months. The remaining 12 patients had on and off pain over the same site with much lesser severity and required membrane-stabilizers for symptomatic relief.

Table 2: Associations in our patients

Bell's palsy	Four patients
Peripheral neuropathy	Old residual AIDP seen in one patient, sub-acute sensori-motor polyneuropathy with lymphocytic pleocytosis in CSF in one patient
Poliomyelitis	Two patients
Ayurvedic treatment	11 patients had greater than one month duration of exposure. One of them had taken for obesity, two for skin lesions, two for acute Bell's palsy and one was recovering from AIDP.

AIDP - Acute inflammatory demyelinating polyneuropathy, CSF - Cerebrospinal fluid

Discussion

Highlights of the present study would be as follows:

1. Largest report from this region of the world, documentation of clinical profile.
2. Pleomorphic clinical presentation, with high incidence of pain and of central features.
3. Associations with previous neurological illness and with preceding ayurvedic treatment.
4. Response to treatment, especially with MPS.

Uncertainty over the natural history of this entity and the absence of diagnostic criteria has caused a large number of names to crop up. Isaacs himself had used the term “continuous muscle fiber activity” (CMFA),^[3] however, presently “neuromyotonia” is the preferred term.^[6] Isaacs’ second report was on an Indian patient in South Africa.^[7] Desai, Pandya and Raju from Mumbai reported repetitive discharges in a patient without clinical activity who developed the same later.^[8] Irani, Purohit and Wadia also from Mumbai suggested that CMFA could arise from anywhere along the peripheral nerve.^[9]

Motor symptoms: Abnormal muscle activities are continuous, gross, often rhythmic, relatively slow undulating movements, occasionally of sufficient force to move small joints and in most cases persistent throughout the period of observation.^[10] Majority of the reported cases have shown persistence of activity during sleep. The movements are generalized but are more prominent over lower limbs (thigh and calf muscles) and shoulders.

Focal forms involving finger (isolated finger flexion), legs and eyes (ocular neuromyotonia, continuous fiber activity of ocular muscles) have also been described.^[11] Ocular CMFA presents with intermittent diplopia and strabismus, is usually idiopathic but might be secondary to radiation, neurovascular compression, Grave’s disease, cavernous sinus thrombosis etc.^[12] Two of our patients had focal form, with movements being restricted to the forearm in one and to the legs in another.

Some patients report muscle stiffness. This primarily affects the distal muscles but may become generalized leading to abnormal posture and gait. There is really no failure on the part of muscle to relax but it is an active contraction of muscle, which is maintained by the continuous muscle fiber activity. This was present in five of

our patients and was not a prominent complaint. There were no specific changes in the deep or superficial reflexes in our patients or in previous reports.

Sensory symptoms: Patients may have severe cramps, squeezing pain or painful paraesthesia.^[13] Occasionally, crawling sensations over skin that were intensified by exercise, nervousness and cold have also been described.^[14] Thigh, calves and shoulder are common sites of these sensory symptoms. Pain was the chief presenting complaint in 19 out of our 20 patients. Pain started in the calf in all the patients, then thigh and then broadly in the ascending pattern. Severity was more in the lower limbs. Pain had similar quality in all patients with constant aches, associated with bursting sensation, occasionally with feeling of crawling insects. This pain was severe enough to disturb sleep.

Central symptoms: In 1890, Morvan described a syndrome of myokymia associated with muscle pain, excessive sweating, weight loss, hallucinations, sleep disorders and behavioral abnormality (Morvan’s ‘fibrillary chorea’ or Morvan’s syndrome).^[4,15,16] This entity might be regarded as a form of neuromyotonia having prominent central features. Twelve of our patients had an anxious look, a peculiar pinched face associated with complaints of irritability and insomnia.

There has been considerable overlap between central and peripheral features in our patients. This is quite understandable, as the basic mechanism of the two manifestations remain the same, that is VGKC abnormality, albeit at different levels of neuraxis. Additionally, there are possibilities that some of the central disturbances result not directly from the autoantibodies, but indirectly from the peripheral effects of the antibodies on secretion of neuro-hormones. This explains the presence of central features in some of our patients and our reluctance to strictly divide the patients on the basis of central and peripheral features.

Associations: Clinical associations with both acquired and inherited diseases has been noted in the literature and has been mentioned in Table 3.^[10]

Neither of our cases was inherited, nor was neoplastic. Two were associated with residual peripheral neuropathy, one of acquired inflammatory demyelinating polyneuropathy and one of a subacute sensori-motor polyneuropathy with lymphocytic pleocytosis in CSF, discussed as possible Lyme’s disease. Four

Table 3: Known associations of neuromyotonia

Acquired	Primary - autoimmune or idiopathic
	Secondary
	(1) Associated with acquired neuropathy, e.g., diabetic
	(2) Autoimmune neuropathies - AIDP, CIDP, penicillamine-induced, primary amyloidosis with serum IgG monoclonal band
	(3) Thymoma with / without myasthenia gravis
	(4) Paraneoplastic - with or without neuropathy e.g., bronchial tumors
Inherited	(5) Toxic/ drug - insecticide, herbicide, alcohol, toluene, gold
	Primary (without neuropathy)
	(1) Autosomal dominant episodic ataxia/ myokymia
	(2) Heredofamilial without overt neuropathy
	Secondary (with neuropathy or other disease)
	(1) Hereditary neuropathies - motor or sensori-motor
	(2) Distal spinal muscular atrophy

AIDP - Acute inflammatory demyelinating polyneuropathy, CIDP - Chronic inflammatory demyelinating polyneuropathy

patients had recent or remote Bell's palsy. This may be considered a significant observation. Two of these patients had also taken ayurvedic treatment in the recent past. The association with ayurvedic treatment in 11 cases was intriguing because of the possibility of toxin-induced neuromyotonia. "Ayurvedic drug" implies the drugs prescribed by the physicians specializing in ancient Indian medical science (Ayurved). The formulations are usually based on herbs, heavy metals and various colloids. We consider this association quite significant because the temporal relationship between prolonged ayurvedic medication intake and onset of symptoms was striking. The symptoms persisted even after withdrawal of ayurvedic medications, suggesting the mechanism to be multifactorial rather than a direct toxic one. The exact toxin could not be identified, as routine heavy metal toxin screens were negative, including lead, mercury, gold or arsenic.

Autoimmunity: There have been reports to suggest autoimmunity and involvement of VGKC in neuromyotonia.^[6,10,17] Evidences include:

1. Clinical association with other autoimmune conditions.
2. Substantial number of patients of neuromyotonia showing increased titer of VGKC antibodies.
3. Reduction in serum anti-VGKC antibodies after plasma exchange, correlating with clinical and electrophysiological improvement.
4. Raised CSF protein and presence of oligoclonal bodies in CSF.
5. Passive transfer studies in mice and *in vitro* electrophysiological experiments both demonstrate that purified neuromyotonia IgG increases neuronal excitability.

Autoimmune theory for causation of neuromyotonia has been proposed for quite some time (Newsome Davis) and experimental proof was given by Singh *et al.*^[17] Haart *et al* in their study of 60 cases presenting with diverse clinical syndromes presenting with peripheral nerve hyperexcitability concluded that autoimmunity was strongly implicated in the pathogenesis and that the EMG features reflect quantitative rather than qualitative differences between them.^[18] Raised protein in CSF is one of the many evidences favoring the autoimmune theory. The cause of raised CSF proteins in autoimmune neurological disorders is still unclear. The mechanism might be dysfunction of blood-cerebrospinal fluid (CSF) barrier; a frequent finding in dys-immune neuropathy. Intrathecal synthesis of immunoglobulins is another proposed mechanism but is still a matter of debate.

GM 1 ganglioside is a constituent of the peripheral nerve membrane and has been implicated as an antigenic target of various autoimmune disorders like Multifocal neuropathy and some cases of GB syndrome.^[19] We had planned to obtain IgG and IgM antibodies against GM1 ganglioside in our patients to search for some additional or alternative autoimmune target (other than VGKC). But for logistic reasons, we were unable to obtain it in all cases. Sera of four patients were subjected to GM1 antibody estimation and titers in three of them were high. The only person tested for VGKC antibody had high titer (1028 pM) and also had high titer of GM 1 ganglioside antibody. Hence the possibility of

an alternative autoimmune target could not be established.

EMG: Our diagnosis depended on characteristic EMG findings in appropriate clinical setting. Electrophysiological findings consisting of the so-called neuromyotonic discharges in the fully developed form were found in all of our patients [Figure 1]. The electrophysiological hallmark is the spontaneous firing of single motor units as doublet, triplet or multiplet discharges that have a high intraburst frequency (usually 150 to 300 Hz).^[5] These discharges are usually found even if there is no visible movement, this was the case in one of our patients. The neuromyotonic discharges are characterized by burst of spontaneous activities having high intraburst frequency, larger burst duration and their waning nature.

Management issues: In his original cases, Isaacs used phenytoin 100mg four hourly with considerable success.^[3] The observation that the acquired form is often associated with an autoimmune disorder and recognition of the role of anti-VGKC in the pathogenesis of the acquired form of CMFA led to the use of steroid, plasmapheresis and intravenous immunoglobulin with varying results. Hudson had reported response to prednisolone.^[10] Mishra *et al* recently reported a case of acquired demyelinating neuropathy leading to neuromyotonia and muscle hypertrophy that has shown response to prednisolone.^[20] Response to high-dose intravenous immunoglobulin and to immunoadsorption plasmapheresis was also reported.^[21-23]

Membrane stabilizers did not provide adequate or rapid relief in our experience. The patients were markedly distressed predominantly by pain, with interference in activities of daily living and in sleep. Besides phenytoin, other drugs were offered at discharge for maintenance therapy including carbamazepine, lamotrigine and topiramate. No specific advantage of any one was found.

MPS has not been tried in the available literature so far. We have used high-dose MPS (1 gm daily, slow infusion for five days) in 19 patients. Patients reported significant symptomatic amelioration of symptoms in all cases. EMG also confirmed

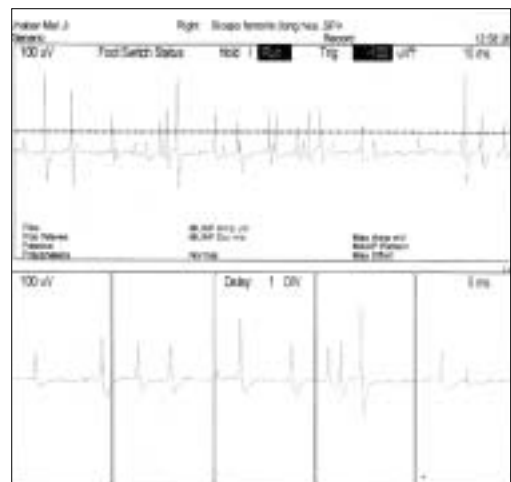


Figure 1: EMG showing bursts of spontaneous activity with fasciculation potentials, doublets and multiplets with intraburst frequency of 200 Hz

reduction of spontaneous activity with only occasional bursts and some fasciculation potentials. Such patients were able to go back to their routine lifestyles, with continuing maintenance therapy of one to three months with single or combination of membrane stabilizing drugs. They are all doing well on follow-up of one to two years.

MPS was chosen for the treatment of our cases for various reasons. It was cheaper than intravenous immunoglobulin and was cheaper as well as easier to administer than plasmapheresis. Another reason for choosing this particular therapy was our reasonably satisfactory experience with this drug for the treatment of dys-immune neuropathies. Finally, its proposed mechanism of action, where it decreases the extravasation of immune cells into the neurons and facilitates the apoptosis of activated immune cells could theoretically benefit in neuromyotonia, hence the selection.

We tried intravenous immunoglobulin (IVIg) in one of our patients with focal form. He had presented with isolated finger flexion of seven months duration and responded dramatically to IVIg. At follow-up of more than two years, he continues to be asymptomatic and electromyographically normal.

Limitations of our study: It would be appropriate to point out certain limitations in our study. For one, it is mainly a clinical documentation of various presentations and associations with response to therapy. We were unable to obtain serum antibodies to potassium channel antibodies for the immunological data. The association with possible toxin exposure in those patients taking ayurvedic treatment could not be further validated.

Conclusions

Mechanisms of origin and cellular immunology of Neuromyotonia are yet to be elucidated with certainty. The involvement of channels other than VGKC may also be predicted, for example the voltage gated sodium channel. The role of toxins having direct effect on these channels is also an area of further research.

It is only after the nosologic limits of this entity are fully delineated that strict criteria can be laid out for diagnosis. Once this happens, then proper therapeutic trials may be envisaged. Neuromyotonia is a heterogeneous condition and can present in varied ways. What led us to present this series is that this not uncommon condition is amenable to treatment and can be easily picked up with a high index of suspicion. Many of these patients will be attending general medicine and psychiatry outdoors because of their diffuse pains and marked secondary anxiety or primary central features. Timely

EMG and ancillary investigations will clinch the diagnosis, so that appropriate therapy with immune modulators and membrane stabilizers may be provided. This individualized therapy can be expected to provide significant relief rapidly in the majority of patients.

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