

Infection-Associated Peripheral Nerve Hyperexcitability: An Under-Recognized Entity

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Abstract

Background: Peripheral nerve hyperexcitability (PNH) and neuromyotonia have been mainly attributed to antibodies against voltage-gated potassium channels (VGKC). Concurrent autoimmune disorders, malignancies, and heavy metal toxicity have also been implicated. There is scarce mention about infection as a triggering factor for PNH. There are no reports of methicillin-resistant *Staphylococcus aureus* (MRSA) infection being a possible precipitating factor for development of PNH. **Methods:** Case series and literature review. **Results:** Four subjects were diagnosed to have features of PNH based on clinical and electrophysiological assessment. All the subjects had concurrent evidence of cutaneous abscesses requiring surgical intervention and antibiotic therapy. The cultures in all of them revealed growth of *Staphylococcus aureus* with three of them being MRSA isolates. Two subjects tested positive for anti-VGKC antibodies. There was remarkable resolution in neuromyotonia after antibiotics in three subjects. One subject succumbed to fulminant MRSA septicemia. **Conclusion:** There appears to be a definitive link between staphylococcal infection (MRSA in particular) and development of PNH. The temporal evolution of PNH associated with the infection and resolution following treatment of the infection does support a causal association. The enterotoxins produced by staphylococci act as superantigens and could trigger an inflammatory cascade along with development of cross reacting antibodies against VGKC in peripheral nerves. Future studies with animal models could provide more directions in this regard.

Keywords: Methicillin-resistant *Staphylococcus aureus*, neuromyotonia, peripheral nerve hyperexcitability, *Staphylococcus aureus*, superantigen, voltage-gated potassium channel

INTRODUCTION

Peripheral nerve hyperexcitability (PNH) comprises a spectrum of neurological disorders ranging from cramp-fasciculation to acquired neuromyotonia.^[1,2] Antibodies against voltage-gated potassium channels (anti-contactin-associated protein-like 2 in particular) have been implicated in neuromyotonia. Infections as a precipitating cause have been hitherto under-recognized and evidence of the same limited to a few case reports. Antigenic epitopes related to infective agents could generate cross reacting antibodies against neuronal ion channels by a mechanism of molecular mimicry.^[1]

We report four cases of neuromyotonia associated with staphylococcus aureus, three of them were documented to have methicillin-resistant *Staphylococcus aureus* (MRSA) infection. Three patients had clinical improvement temporally related with appropriate antibiotic therapy and adequate surgical drainage. One patient succumbed rapidly to MRSA septicemia and shock. Enterotoxins produced by MRSA are known to act as superantigens which could have led to an inflammatory response with cross reacting antibodies causing PNH. This association between MRSA infection and neuromyotonia has not been previously described in literature to the best of our knowledge.

CASE SERIES

Case 1

A 41-year-old gentleman with no prior comorbidities, presented with progressively increasing complaints of

burning sensation of feet and hands and twitching of muscles of lower limb of 2 weeks duration. He also noted low grade fever with skin lesions over the right leg and left thigh 1 week prior to presentation. There was decreased sleep and orthostatic intolerance. No motor weakness or sensory loss was noted. There was diffuse twitching of muscles noted mainly in the lower limbs [Video 1]. Routine nerve conduction was normal. There were after discharges noted on electrical stimulation of the nerves [Figure 1]. Needle electromyography revealed fasciculations, doublets, triplets, and multiplets motor unit discharges [Figure 2]. Blood counts and erythrocyte sedimentation rate (ESR) were normal. Cutaneous abscesses were noted and incision

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Submitted: 09-May-2020 **Revised:** 21-May-2020 **Accepted:** 27-May-2020

Published: 28-Apr-2021

Videos available on: www.annalsofian.org

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DOI: 10.4103/aian.AIAN_427_20

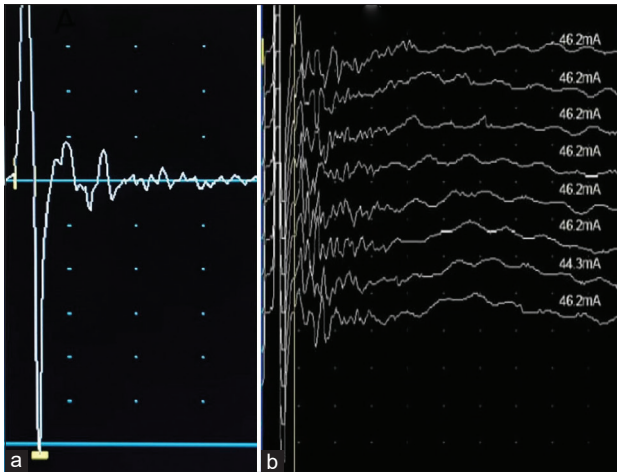


Figure 1: Supramaximal stimulation of the tibial nerve with demonstrable after discharges (a) Following M wave and (b) following F wave. Time base: 20 ms, sensitivity 500 μ V

drainage of the abscesses was done. The smear revealed growth of gram positive cocci in pairs and culture revealed MRSA. Blood cultures were sterile. There was no evidence of any malignancy on positron emission tomogram. Serum voltage-gated potassium channels (VGKC) (anti-CASPR 2) antibodies were positive (Euroimmune kit with use of immunohistochemistry and transfected HEK 293 cells). He was started on antibiotics (vancomycin for 2 weeks, followed by linezolid for 4 weeks). He became afebrile and twitching of muscles had also reduced at the time of discharge at 2 weeks [Video 2]. There was complete resolution of neuropathic pain. At time of follow-up after 12 weeks, he had completely improved and repeat serum VGKC antibody was negative. Symptomatic medicine (carbamazepine) was subsequently tapered.

Case 2

A 72-year-old gentleman with no prior comorbidities presented with difficulty in walking with associated pain in the lower limbs for 10 days duration. There were also complaints of insomnia and nocturnal hallucinations (suspected Morvan's syndrome). On examination, he was febrile and noted to have weakness of the proximal and distal lower limb muscles (Grade 2 MRC proximal and Grade 3 MRC distal). Diffuse twitching was noted in the lower and upper limbs. Deep tendon reflexes were normal. Nerve conduction studies revealed reduction in both compound motor action potentials and sensory nerve action potentials. Electromyogram (EMG) was consistent with neuromyotonia. Blood counts and ESR were normal. Serum creatine kinase was 1272 U/L. A Positron emission tomography- computed tomography (PET-CT) did not show any evidence of neoplasm. In view of excruciating pain and weakness, plasma exchange was started; however, he continued to have persisting symptoms. Serum VGKC antibodies were positive (radioimmunoassay- 257 pmol/L, normal 0-85). During the course of hospitalization, he was noted to have a carbuncle on the back. He was taken up for

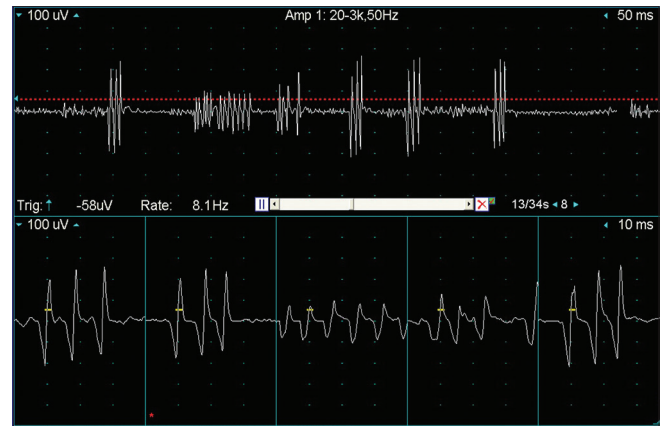


Figure 2: EMG of *gastrocnemius* with demonstration of triplet and multiplet motor unit discharges. Time base: 50 ms and sensitivity 100 μ V

debridement of the same and culture grew methicillin-sensitive staphylococcus aureus. He was treated with cloxacillin and had resolution in symptoms at follow-up visit after 6 weeks.

Case 3

A 44-year-old gentleman previously diagnosed to have myasthenia gravis, post-operative status thymectomy with an invasive thymoma presented with new onset severe burning paresthesias of feet with twitching of muscles noted over the calves bilaterally of 1 week duration. He also reported swelling over the face with pain, features consistent with an abscess. Clinical and electrophysiological features were consistent with neuromyotonia. Drainage of the facial abscess revealed growth of MRSA. He was started on linezolid following which there was improvement in muscle twitching and he became asymptomatic. He subsequently received chemotherapy for his invasive thymoma.

Case 4

A 33-year-old gentleman presented with diffuse pain all over the body with twitching of muscles for 20 days. He had been on native medicines for right-sided hemiparesis which he had developed 3 years ago after a traumatic brain injury. He also was noted to have multiple painful subcutaneous swellings all over the body. He had mild dyspnea at presentation which worsened during hospitalization. Electrophysiological features were consistent with neuromyotonia. Surgical drainage of the abscess grew MRSA. However, he had features of disseminated infection and succumbed to acute respiratory distress syndrome and septic shock. Heavy metal screen had also revealed mildly elevated lead levels (27.8 mcg/dl, normal <10 mcg/dl).

DISCUSSION

Neuromyotonia is a syndrome of PNH characterized by visible muscle twitching (myokymia), cramps and impaired muscle relaxation (pseudomyotonia).^[1,2] The syndrome was fully described first by Issacs in 1961. Muscle twitching could be visible/palpable as a wave-like rippling of muscles

under the skin involving the limbs, trunk, or even the face. Cramps could be painful, associated with spasms, and worsen with voluntary contraction. Muscle stiffness, hypertrophy, weakness, and impaired relaxation could also occur. Severe neuropathic pain has also been reported. Increased sweating and insomnia are common features. At times, hallucinations and delusions suggest central nervous system involvement referred to as Morvan's syndrome. Electromyogram shows presents of spontaneous discharges in the form of continuous, irregular doublet, triplet, or multiplet motor unit discharges at high intraburst frequency (30–300 Hz). After discharges can be visualized after supramaximal electrical stimulation of the nerve. The neuromyotonic discharges persist during sleep, general anesthesia, and get partially suppressed following local anesthetic nerve blocks.^[1,2]

An autoimmune etiology has been proposed and antibodies against VGKC have been implicated in the majority (nearly 40%).^[1] Neuromyotonia has been more associated with anti-CASPR 2 than anti-leucine-rich glioma-inactivated 1 (LGII) antibodies.^[3] This is attributable to higher expression of CASPR 2 in peripheries. Concurrent autoimmune disorders have been documented in as high as 50%. These include myasthenia gravis, autoimmune thyroiditis, inflammatory neuropathies, rheumatoid arthritis, systemic lupus erythematosus, and vitiligo. Malignancies associated include thymoma, small cell lung cancer, and lymphomas.^[1] Features of neuromyotonia could also occur in hereditary channelopathies and inherited neuropathies. Heavy metals could also predispose to anti-VGKC triggered autoimmunity by direct damage to peripheral nerve terminals.^[4,5] This subset is characterized to have severe neuropathic pain in case series.^[5] Drugs like penicillamine and gold are alternate provoking agents.^[1] Symptomatic treatment with anticonvulsants like phenytoin, carbamazepine, lamotrigine, and sodium valproate has been proven to be beneficial. Plasma exchange may provide benefit lasting up to 4 weeks. Corticosteroids and steroid sparing agents may also be required.^[1] Malignancies if associated need to be treated appropriately.

Infection as a cause of neuromyotonia has been rarely reported in literature with evidence limited to a few case reports. Ocular neuromyotonia has been reported following mucormycosis and resultant cavernous sinus thrombosis.^[6] Maddison *et al.* had reported the case of a 52-year-old gentleman with neuromyotonia with altered sensorium and quadriparesis. On evaluation, he was found to have epidural abscess and hydrocephalus, *Staphylococcus aureus* being the offending infective agent.^[7] He clinically responded to surgical drainage and antibiotic therapy. There was also disappearance of anti-VGKC antibodies. Liu *et al.* reported a case with persistent fever and continuous muscle fiber activity in whom a scrotal abscess was subsequently detected and there was a dramatic improvement a few days after drainage of the abscess.^[8] Culture grew *Staphylococcus aureus*. There was a similar report of *Staphylococcus* associated neuromyotonia by Diaz in 2002.^[9] Cases following upper respiratory infection have also been mentioned.^[10]

The spectrum of infections associated with staphylococcal infections includes cutaneous abscesses, osteomyelitis, endocarditis, scalded skin syndrome, and toxic shock syndrome.^[11] Microbial surface components could act as virulence factors. In addition, enterotoxins, cytolysins, exfoliative toxins, toxic shock syndrome toxin 1, cytolysins, and Panton–Valentine leucocidin are also secreted.^[12] Superantigens are protein components secreted by bacteria which potentially activate CD 4+ T cells by directly binding to Major Histocompatibility complex (MHC) class II molecules of antigen presenting cells. There is T cell activation and cytokine production (Interleukin 1, IL-2, IL-6, tumor necrosis factor α and interferon γ) eventually leading to polyclonal B cell activation and immune complex deposition.^[11,12]

Nasal carriage of *Staphylococcus aureus* has been identified in nearly 30% of normal population and associated with higher relapse risk in Wegener's granulomatosis.^[13] Peptide component of *staphylococcus aureus* have been identified to be homologous to myeloperoxidase (MPO) T cell epitope and induce anti-MPO autoimmunity.^[14] Other associations include Henoch–Schönlein purpura, post infective glomerulonephritis and rheumatoid arthritis.^[15,16] Neurological disorders with staphylococcal association include multiple sclerosis and Guillain–Barre syndrome though a definite causal association has not yet been proven.^[17,18]

The possible pathophysiology in the presented cases would be infection associated autoimmunity resulting in cross-reacting antibodies targeted against the neuronal voltage-gated ion channels resulting in PNH. The model would be similar to inflammatory neuropathies like Guillain–Barre syndrome. The transient appearance of anti-CASPR2 antibodies and subsequent disappearance after optimal treatment of the infection as illustrated in case 1 supports the hypothesis. A direct toxin effect on nerve terminals is another possibility considering the concurrent presentation along with infection. “Molecular mimicry” and “epitope sharing” appear to be the most plausible theories with a dysregulated immune response secondary to non-specific activation of autoimmune cells (“bystander activation”).^[19] Use of steroids and other immunosuppressants could be deleterious in the presence of active infection. Plasma exchange and intravenous immunoglobulin could be helpful if there is ongoing disease activity secondary to a persistent autoimmune response. The role of these modalities in treatment regimens will need further evaluation in prospective studies.

Limitations include the fact that testing for antibodies against VGKC complex was not done in the latter two subjects and could be repeated in only one subject as we had limited access to the antibody tests during their time of presentation. One subject each had concomitant thymomatous myasthenia gravis and heavy metal exposure respectively in addition to documented MRSA infection again emphasizing a multifactorial causation. However, the unequivocal demonstration of a fairly dramatic improvement in neuromyotonia following optimal treatment of staphylococcal infection supports the hypothesis of infection triggered PNH.

CONCLUSION

The case series provides a fascinating insight into another neurological disease (PNH) with an infectious trigger (*Staphylococcus aureus*) for autoimmunity. It is highly likely that staphylococcal infections with associated neuromyotonia have been under-recognized. As immunosuppression has been conventionally considered a therapeutic modality in neuromyotonia, there appears to be a case for meticulous screening for any occult infections which actually could have been the precipitating factor. Future prospective studies could incorporate detailed immunological tests including cytokine assays and lymphocyte subset analysis. Appropriate animal models could also help in further identifying the antigenic trigger and further elucidating the pathophysiology.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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