Journal of Neurology & Experimental Neuroscience

https://doi.org/10.17756/jnen.2019-061

Case Report

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Case Report: Length-dependent Small Fiber Polyneuropathy Caused by Coxsackie and Influenza Virus Co-Infection

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Received: May 31, 2019
Accepted: December 15, 2019
Published: December 17, 2019

Citation: Tsakadze N, Catania J, Hoffmann M, Benes-Lima L, Estevez AG, Franco MC, Rossi F. 2019. Case Report: Length-dependent Small Fiber Polyneuropathy Caused by Coxsackie and Influenza Virus Co-Infection. *J Neurol Exp Neurosci* 5(2): 103-105.

Published by United Scientific Group

Abstract

We describe a 34-year-old woman with an acute length-dependent small-fiber polyneuropathy (SFP) caused by Coxsackie B3 and B5 and Influenza A, H3N2 viruses. She presented with an acute onset of burning pain and distal sensory deficit in both legs shortly after the acute viral encephalopathy. This is the first report of the serologically confirmed length dependent SFP caused by Coxsackie and Influenza viruses.

Keywords

Small-fiber polyneuropathy, Coxsackie virus, Influenza virus

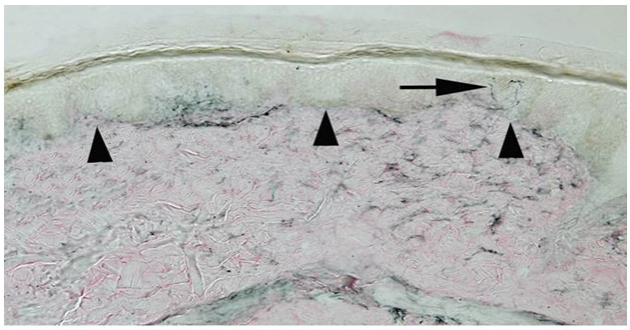
Introduction

Small fiber polyneuropathy (SFP) selectively affects small myelinated or unmyelinated nerve fibers involved in pain and temperature sensation and autonomic function. SFP commonly presents with a variety of sensory complaints (paresthesias, brief electrical shocks, burning pain, etc.) in a length-dependent distribution, affecting predominantly the feet, and to a lesser degree - the hands. Rarely, SFP presents in a non-length dependent pattern, affecting focal areas of the body. SFP may also cause the autonomic dysfunction, affecting different organs. SFP has diverse range of etiologies, including several infectious agents, but remains idiopathic in up to 50% of cases. We report a rare case of length dependent SFP caused by Coxsackie and Influenza virus co-infection.

Case Report

34-year-old black female was hospitalized with fever of 102.4°F and acute encephalopathy. She developed an upper respiratory infection 5 days prior to admission, progressively became more lethargic and then unresponsive. Soon after her mental status cleared, she developed constant incapacitating burning pain in her hands and feet and was unable to bear weight on her feet. She denied symptoms of autonomic dysfunction. She had a history of well-controlled diabetes (last HgBA1C was 5.7) and rheumatoid arthritis but denied any sensory symptoms or any limb discomfort prior to this hospitalization. No history of HIV, unhealthy consumption of alcohol, illicit drug use, chemical exposure, kidney or liver disease. Family history was negative for peripheral neuropathy. Physical examination on admission showed altered mental status, confluent rash on chest and abdomen, but no organomegaly

or enlarged tonsils. Serology was positive for Coxsackie virus B3 and B5 with titers ≥ 1:640 and 1:80 [normal < 1:10], respectively and Influenza A, H3N2. Convalescent sera were available for comparison of titers to be able to differentiate between current and past infection with these viruses. Nasopharyngeal respiratory PCR was positive for influenza A, H3N2. Other relevant labs included elevated ALT 77 and AST 351 [normal ALT 4-51; AST 5-46], respectively, low sodium 127, elevated CPK (8265, on discharge - 476) [normal 24-200] and elevated ANA at 1:1280 with a speckled pattern. Porphyria, celiac and thyroid panel, as well as vitamins B12, B1, B6 and ACE levels were all normal. Blood serology was negative for HIV, Lyme, hepatitis, West Nile virus. EBV serology was consistent with prior infection. Serum PCR was negative for Adenovirus HHV6, and Parvovirus B19. Lumbar puncture showed elevated opening pressure of 27 cm of water. CSF analysis revealed WBC 61 (52 % neutrophils), RBC 12, glucose 56, protein 325. CSF cultures and Cryptococcal Ag were negative. CSF PCR was also negative for HSV-1 and 2. CT head and MRI brain were unremarkable. EEG showed generalized slowing without epileptiform activity. Pain remained chronic and incapacitating after the discharge, and was partially relieved by imipramine, but failed to respond to pregabalin, gabapentin, nortriptyline, and opioids. Nerve conduction study was done six weeks after the onset of her encephalopathy, it showed reduced amplitude of the right sural nerve sensory action potential (2μV), while left was unrecordable. Motor nerve action potentials in upper and lower extremities were unremarkable. General physical examination after discharge was unremarkable. Neurologic examination showed normal mental status, cranial nerves, coordination, motor strength and reflexes. Pain and temperature sensation were decreased in both feet in stocking distribution; vibration and proprioception were normal. Skin biopsy from the right thigh and right calf skin showed significant reduction in the epidermal nerve small fibers density and confirmed the diagnosis of SFP (Figures 1 and 2) and showed no evidence of vasculitis or amyloidosis.



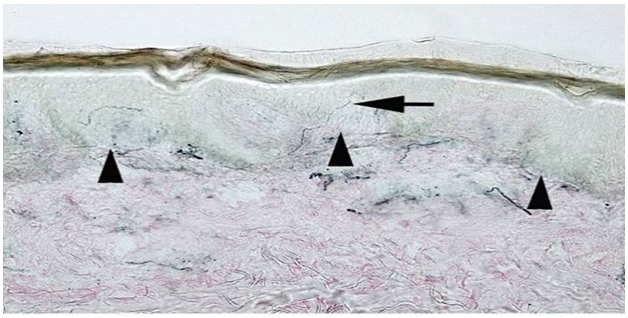
Right calf skin biopsy showing significant reduction in epidermal nerve fiber density. Vertical arrows point to location of dermal-epidermal juncture. Horizontal arrow points to unmyelinated or poorly myelinated nerve or terminal nerves. Images have been captured at 20X magnification.

Image provided as a courtesy of Therapath Neuropathology

Figure 1: Biopsy samples with a dramatic decline in small-fiber density.

Discussion

SFP selectively affects peripheral afferent thinly myelinated Aδ and unmyelinated C-fibers which convey pain



Right thigh skin biopsy showing a significant reduction in epidermal nerve fiber density. Vertical arrows point to location of dermal-epidermal juncture. Horizontal arrow points to unmyelinated or poorly myelinated nerve or terminal nerves. Images have been captured at 20X magnification.

Image provided as a courtesy of Therapath Neuropathology

Figure 2: Biopsy samples with a dramatic decline in small-fiber density.

and temperature sensation and are also involved in autonomic function (sudomotor, thermoregulatory, cardiovascular, gastrointestinal, urogenital) [1,2]. Clinically, SFN presents with two clinical patterns: length-dependent SFN (predominantly affects the feet) and non-length dependent SFN (impairment of one or multiple nerves with a sensory patchy distribution on the face, upper limbs, or trunk). Clinical presentation involves mainly sensory (both positive and negative) and autonomic symptoms. Individuals present with pain, burning or electrical shock-like, allodynia, and hyperesthesia. Cramps, restless leg and foot movements may also occur. Autonomic symptoms may include abnormal sweating, postural lightheadedness, syncope, dry eyes and dry mouth, alternating diarrhea/constipation, early satiety, urinary frequency, and impotence. Examination is usually normal, except for signs of small fiber loss (decreased or absent temperature and pinprick sensation) and occasionally erythromelalgia (red skin). Sensory and motor nerve conduction studies are unremarkable, however large nerve fibers may also be co-affected, like in this case. Gold standard for diagnosis is skin biopsy displaying a reduction in intraepidermal small nerve fiber density (as shown in the pictures). Etiological factors are diverse and include toxic, metabolic, infectious, autoimmune, paraneoplastic, and genetic causes. In up to 50 % of cases etiology remains elusive. Among the infectious etiologies, HIV, hepatitis C and B, Chagas disease, leprosy, Lyme, influenza, Coxsackie, herpes and varicella viruses have been reported, but are exceedingly rare. Coxsackie B virus has been reported only once in association with autonomic neuropathy [3]. Likewise, there is only single report of the autonomic neuropathy caused by influenza. H1N1 [4], Although the reported patient had history of diabetes, it is well controlled and there were no clinical symptoms suggestive of polyneuropathy prior to her acute illness.

However, her nerve conduction studies revealed an underlying asymptomatic length-dependent sensory predominant axonal-loss polyneuropathy. Authors suspect that this axonal-loss polyneuropathy was already present before the acute illness and might have been a risk factor to develop the painful small-fiber polyneuropathy. Thought, authors cannot rule out that big myelinated fibers were also damaged or partially damaged from the original viral

infection. Therefore, although we cannot entirely rule out the potential confounding role of diabetes in this case, we believe that acute presentation in the context of infection points more to the infectious etiology as the leading etiological factor. Of note, she had a transitory elevation in her CPK most likely triggered by Coxsackie B and influenza virus induced-viral myositis, as previously reported [5]. The current is the first report of Coxsackie and/or Influenza viruses causing length dependent SFP, separately or in combination. Treatment of the SFP includes symptomatic management of neuropathic pain (pregabalin, gabapentin, duloxetine, tricyclics, topical lidocaine, opioids [6] and disease-modifying therapies, such as IVIG and steroids [1, 2].

In summary, this is the first case report of a length dependent acute SFP caused by a combination of the Coxsackie and Influenza viruses.

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