CASE REPORT

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Spinocerebellar Ataxia 3 (SCA3) Patient with Peripheral Neuropathy

Siti Aminah,[1] Iin Pusparini,[1] Nushrotul Lailiyya,[1] Ahmad Rizal Ganiem,[1] Uni Gamayani,[1] Yusuf Wibisono,[1] Fathul Huda,[1,2] Yunia Sribudiani,[3,4] Tri Hanggono Achmad,[3,4]

[1]Department of Neurology, Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital Bandung, Indonesia
[2] Division of Physiology, Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Indonesia
[3]Division of Biochemistry and Molecular Biology, Department of Biomedical Sciences, Faculty of Medicine Universitas Padjadjaran, Bandung, Indonesia
[4]Research Center of Medical Genetics, Faculty of Medicine Universitas Padjadjaran, Indonesia

Abstract

Spinocerebellar ataxia (SCA) 3 is a neurodegenerative disease which involves cerebellum and extra cerebellum. Neuropathy in SCA3 manifests in various ways, including axonal and demyelination lesions in sensory and motor nerves. There has not been any study that describes the peripheral neuropathy characteristics of SCA3 patients in Indonesia at the time of this publication. This paper reports a case of a 43-year-old male with known spinocerebellar ataxia 3 presented with hereditary ataxia and mild numbness in both palms since two years before. No abnormalities were found during the sensory examination. The NCS showed severe axonal demyelinating sensorimotor peripheral neuropathy. In magnetic resonance imaging (MRI), an atrophy in the cerebellum with cerebral multiple lacunar infarction was identified. Electrophysiological results revealed profound axonal lesion in peripheral nerves. To conclude, peripheral neuropathy in SCA3 represents the dominance of axonal lesions in motor nerves.

Keywords: NCS, peripheral neuropathy, SCA3

Introduction

SCA3 is a genetically neurodegenerative disorders which has wide spectrum of signs and symptoms. Pathophysiologically, SCA3 involves the cerebellum, its afferent, and efferent pathways. SCA3 is categorized as trinucleotide repeat disorders which caused by unstable Cytosine Adenine Guanine (CAG) trinucleotide repeat thus causing abnormal lengthening polyQ. This led to neurotoxicity and death cell. SCA3 is characterized predominantly by ataxia followed by other neurological signs, including pyramidal and extrapyramidal dysfunction, bulbar, spinal, oculomotor disturbances, cognitive impairment, and peripheral nervous system involvement.[1] The first symptom in SCA3 typically is gait difficulty. Sensory complaint has been stated 3% preceding ataxic symptoms.[2] Peripheral nerve is said to be a frequent site of the degenerative process in SCA3. Generally, peripheral nervous system involvement was found in 70% of patients with SCA. Patients with SCA3 revealed neuronopathy and axonopathy as part of peripheral nerve involvement.[3]

The nerve conduction study (NCS) is a noninvasive gold standard test to identify peripheral nerve impairment.[4] NCS study can accurately diagnose any neuropathy by confirming the potential location damage which cause altered sensations. Although peripheral neuropathy was commonly alluded in SCA3 as constant features however have not been revealed clearly yet in literature. Moreover, in Indonesia, trinucleotide repeat diseases, like SCA3 has never been reported previously. Hence, here we reported for the first time a case of a SCA3 patient with peripheral neuropathy in Indonesia.

Corresponding Author:
Siti Aminah,
Department of Neurology, Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia
Email: aminahdr@yahoo.co.id

Case

A 42-year-old male, with known spinocerebellar ataxia 3, presented in his 34th year with ambulating difficulty described as a wide-based gait. He also complained for frequently falling and had difficulty for reaching objects because of hand tremors. For six years, his incoordination was deteriorated. He was barely able to take a few steps with bilateral walking aid, usually using a wheelchair. The gait disorder was followed by scanning speech, dysarthria, difficulty in swallowing, and vertigo. Two years later, he developed mild numbness on bilateral palms and frequent cramps on his both thighs. There were no abnormalities in hearing or vision. The patient has never been examined and treated by medical profession previously. He denied any history of chronic diarrhea, hypertension, hyperthyroid, diabetes mellitus, alcohol consumption, malignancy, and autoimmune diseases which were established by physician before. He also declined for any chronic consumption of specific drugs which related to neuropathy as the adverse effects.

Family history was obtained. Affected individuals were drawn in family pedigree (Figure 1). The arrow sign showed proband (IV.8). Proband had grandmother (II.1), father (III.1), aunty (III.5), uncle (III.8), sisters (IV.1 and IV.3), and brothers (IV.5 and IV.7) with gait disturbance history since young age. On neurologic examination, we observed nystagmus gaze evoked, slight left facial and hypoglossal nerve palsy, dysarthria, and dysphonia. His musculoskeletal system showed bilateral wasting of the biceps, deltoid, and quadriceps muscles. Fasciculation was not found. Pinprick sensation was normal. Vibration and position were not disturbed. Tendon reflexes were increased in upper and lower limbs. Romberg's sign and sharpened romberg's sign were positive. Tandem walking test was strongly positive. Pathological reflexes were absent. Trunk ataxia, dysmetria, and intention tremor were revealed. To stratify neuropathy grades, we used Toronto Clinical Neuropathy Score (TCNS).[5] This patient had score 2 which indicated no neuropathy based on clinical setting. We also used the Scale for the Assessment and Rating of Ataxia (SARA) to measure the severity of ataxia.[6] This patient had score 15.5 which indicated moderate ataxia.[7] For nonataxia assessment, we used Inventory Nonataxia Signs (INAS) to identify if nonataxia signs were existed. This clinical instrument helped to assess disability in ataxia patient because extracerebellar deficits often exacerbated ataxia symptoms.[8] Nonataxia signs were presented in this patient based on this scale.

Brain MRI demonstrated early of atrophy sign in the cerebellum concomitant with multiple lacunar infarction in bilateral periventricular, predominant in right side (Figure 2).

Upper and lower limb NCS results were as follows: for the right peroneal (figure 4A) and

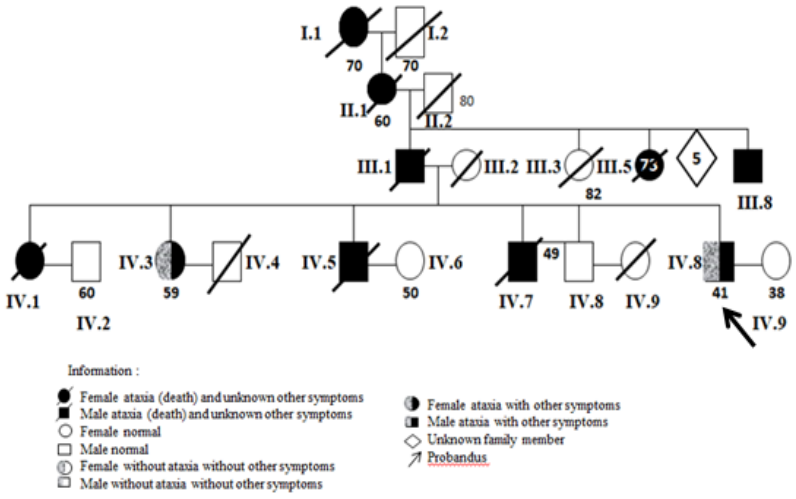

Figure 1 The Pedigree of Clinically Suspected ADCA Family

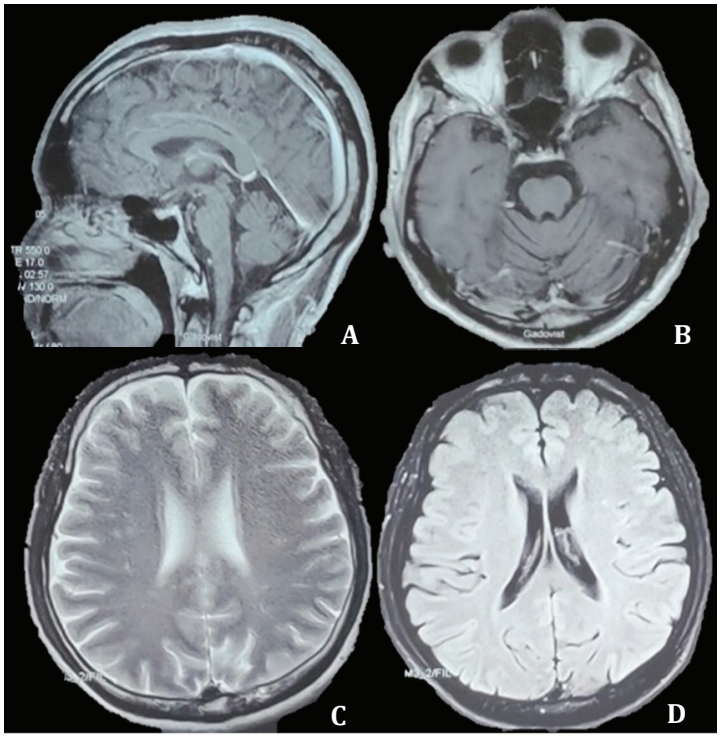

Figure 2 Brain MRI Sagittal and Coronal View: Widening of the Plica is Suggestive of Early Signs of Cerebellar Atrophy

(A,B) with multiple lacunary infarctions in the periventricular bilaterally, particularly on the right side (C,D)

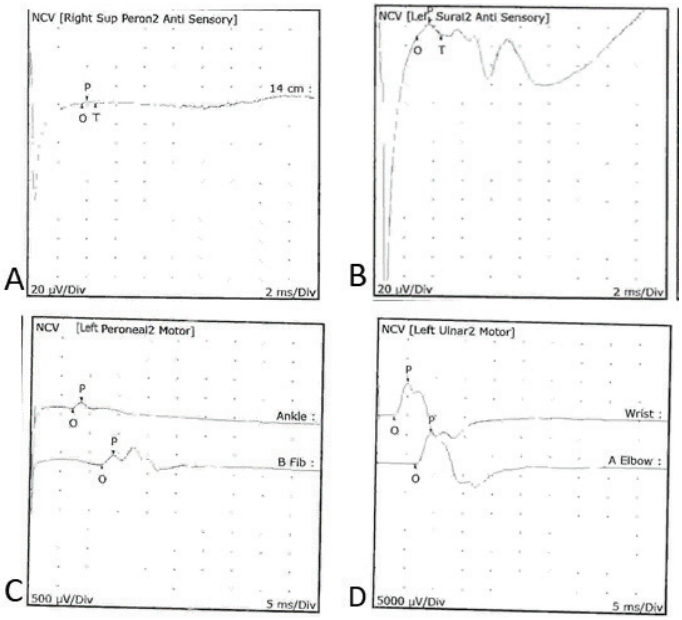

Figure 3 Nerve Conduction Study Results for the Case

(A) No response SNAP on right peroneal nerve; (B) Attenuated SNAP amplitude on left sural nerve; (C) Attenuated CMAP amplitude on left peroneal nerve; (D) Attenuated CMAP amplitude on left ulnar nerve

right sural nerve, no response sensory nerve action potential (SNAP) were detected; for the left sural nerve, the SNAP amplitude was attenuated (Figure 4B); for the left median nerve, reduced compound muscle action potential (CMAP) amplitude and prolonged distal latency were observed; for the left peroneal (Figure 4C), left ulnar (Figure 4D), and right ulnar nerves, decreased CMAP amplitude were seen; and for the left tibial nerve, prolonged distal latency of CMAP was revealed. This NCS results suggested no response in right peroneal and sural nerves; axonal lesion of the left sural, left motor peroneal, left motor ulnar, and right motor ulnar nerves; demyelinating lesion of the left tibial nerve; and axonal demyelinating lesion of the left median motor nerve. Needle Electromyography (EMG) was not performed. Ultimately, based on neurological examination of typical signs and NCS, he was diagnosed with peripheral neuropathy.

Discussion

SCA3 has not addressed the incidence of subclinical peripheral nerve involvement systemically. SCA3 was identified in this patient by patient's clinical complaints, family history, physical examination, genetic testing, MRI, and NCS. The assessment of neuropathy may aid in determining the extent and course of SCA3. This report showed an evidence for the existence of the extracerebellar symptom of SCA3. The typical MRI findings in individuals with SCA3/MJD were cerebellar atrophy, which was similar to our instance. Peripheral nerves are often affected in SCA3 and can be quantitatively assessed by neurophysiological test, such as NCS. Based on NCS examination, SCA 3 showed peripheral neuropathy which was classified into axonal, demyelinating, and mixed neuropathy in sensory, motor, and sensorimotor nerves. In Warrenburg et al study, electrophysiological evidence of peripheral nerve involvement was found in 70.3% of SCA patients.[3] Whilst, in a multicentre EUROSCA study, neuropathy was clinically seen 84% in patients with SCA3. However, it was 55% electrophysiologically.[9]

SCA3 is caused by the expansion of the CAG repeat resulting in the mutant protein ataxin-3 containing the expansion of the polyQ chain. This aggregation of the protein ataxin-3 causes inclusions in the nerve cell. Axonal aggregates are widespread not only in the central nervous system, but also in the peripheral nervous system due to the susceptibility of the peripheral nervous system to polyQ toxicity. The possible mechanisms involving the peripheral nervous system are dysfunction of the dorsal roots, anterior horn nerves, axonopathy, or myelinopathy.[3,12-15] The pattern of the neuropathy in this case more predominantly axonal lesion in both sensory and motor nerves, rather than demyelination. This evidence showed that peripheral neuropathy might affect axons due to impaired axonal transport due to inclusion bodies of ataxin-3 in the axons. Demyelination is likely due to ataxin-3 aggregate in Schwann cells.[15,16] Axon loss causes loss of amplitude of nerve action potentials and myelin loss results in prolonged distal latencies and slowed conduction velocities in NCS. The nerve conduction study results in previous studies demonstrated sensorimotor axonal demyelinating neuropathy in SCA3, with some also showing a minor to severe degree of axonal loss.[3, 10-13] In metabolic causes, the most distal part of the axons usually degenerates first, with concomitant breakdown of the myelin sheath, which as known as "dying-back" or length-dependent neuropathy.[16] In contrast, genetic causes may affect myelin diffusely or axon initially with intact myelin, with a slowly progressive course.[17] This case report suggested an existence of peripheral impairment in SCA3 with the dominance of axonal lesion in motor nerves. In a prior study, electrophysiological evidence of an axonal sensorimotor polyneuropathy, a motor or sensory neuropathy, or normal results was found in SCA3 individuals with symptoms or indications of peripheral neuropathy.[3] Neuropathy may be detected electrophysiologically before symptoms appear.[18] SCA3 individuals, according to Graves and Guiloff,[19] had a progressive axonal, distal, symmetric sensory polyneuropathy with a cerebellar syndrome six years later.[19] Patients with SCA3 who develop polyneuropathy may suffer a late-onset ataxic condition, according to Lau et al.[20] As a result, when treatment were available, early SCA3 symptoms might be a potential method for later therapy management. Additionally, in SCA3, the proclivity for axonal or demyelinating lesions, or motor and sensory fiber damage, has not been publicly known. As a result, a larger-scale investigation with a larger sample size may be required in the future. Complete metabolic panel, hemoglobin A1C, vitamin B12 level, and thyroid function tests have not been yet performed in this patient in order to rule out other risk factors for neuropathy and to determine the likelihood of other comorbidities that might aggravate neuropathy. Nonetheless,

the axonal neuropathy pattern may be linked to the SCA3. Sural nerve biopsy may validate this condition, which also contributes to this case report's limitations.

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