Clinical Case Report

Medicine®

OPEN

Spastic paraparesis caused by X-linked adrenoleukodystrophy mimicking vacuolar myelopathy in a human immunodeficiency virus patient

A case report

Jin-Sung Park, MD[a,b], Donghwi Park, MD[c,d,*]

Abstract

Rationale: Vacuolar myelopathy is one of most common cause of spastic paresis in patients with human immunodeficiency virus (HIV) infection. However, X-linked adrenoleukodystrophy (X-ALD), which is a metabolic disorder caused by impairment of peroxisomal beta-oxidation of very-long-chain fatty acids (VLCFA), also manifests as various neurological deteriorations including adult onset spastic paraparesis. To the best of our knowledge, there has been no report of newly developed spastic paresis due to X-ALD in a patient with HIV infection.

Patient concerns: A 30-year-old male had presented with progressive spastic paraparesis for 1 year.

Diagnosis: X-ALD.

Intervention: Brain and spine magnetic resonance imaging (MRI), VLCFA, and genetic test.

Outcomes: His spinal MRI mimicked vacuolar myelopathy, but he was finally diagnosed with X-ALD using the VLCFA and genetic test.

Lessons: Although rare, isolated spastic paraparesis can occur in HIV patients; additional tests such as VLCFA can be useful for the differential diagnosis. More data are needed to understand the pathological mechanisms underlying the two diseases.

Abbreviations: AMN = adrenomyeloneuropathy, CSF = cerebrospinal fluid, HIV = human immunodeficiency virus, HNP = herniated nucleus pulposus, MRI = magnetic resonance imaging, PCR = polymerase chain reaction, SEP = somatosensory evoked potentials, VLCFA = very-long-chain fatty acids, X-ALD = X-linked adrenoleukodystrophy.

Keywords: human immunodeficiency virus, spastic paraplegia, very-long-chain fatty acids, X-linked adrenoleukomyelopathy

1. Introduction

Vacuolar myelopathy is a chronic myelopathy associated with human immunodeficiency virus (HIV) infection. It is predominant in HIV patients with low CD4 cells and clinically manifests as neurological symptoms such as spastic paraparesis, urinary incontinence, and erectile dysfunction. Spinal magnetic resonance imaging (MRI) typically reveals spinal cord atrophy or intrinsic cord signal abnormalities.[1–3] The pathogenesis of vacuolar myelopathy must be elucidated, but it is presumed that HIV directly affects the myelin, causing demyelination, which was observed in an autopsy study.[4] However, X-linked adrenoleukodystrophy (X-ALD), which is a metabolic disorder caused by impairment of peroxisomal beta-oxidation of very-long-chain fatty acids (VLCFA), also manifests as various neurological deteriorations including adult onset spastic paraparesis. To the best of our knowledge, there has been no report of newly developed spastic paresis due to X-ALD in a patient with HIV infection. Here, we report a rare case of isolated spastic paraparesis in X-ALD that mimicked vacuolar myelopathy. The clinical data and images were obtained with informed consent of the patient including consent to use the photographs in this report, according to the Declaration of Helsinki.

Editor: N/A.

Disclosure: This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT, and Future Planning (NRF- 2017R1D1A1B03033127). This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (Ministry of Science and ICT) (No. 2017R1C1B5076264).

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit upon the authors or upon any organization with which the authors are associated.

The authors have no conflicts of interest to disclose.

[a] Department of Neurology, [b] Department of Neurology, Kyungpook National University Chilgok Hospital, [c] Department of Rehabilitation Medicine, Daegu Fatima Hospital, [d] Department of Phamacology, Kyungpook National University School of Medicine, Daegu, Republic of Korea.

[*] Correspondence: Donghwi Park, Department of Rehabilitation Medicine, Daegu Fatima Hospital, Ayangro 99, Dong gu, Daegu 41199, Republic of Korea (e-mail: bdome@hanmail.net)

Medicine (2018) 97:20(e10756)

Received: 19 February 2018 / Accepted: 25 April 2018

http://dx.doi.org/10.1097/MD.0000000000010756

2. Case

A 30-year-old man had presented with progressive spastic paraparesis for 1 year. He was diagnosed with HIV 5 years prior to his visit to the neurology outpatient clinic and was on regular antiviral medication. The patient underwent anterior cervical discectomy and fusion (ACDF) surgery after a diagnosis of cervical herniated nucleus pulposus (HNP) as the cause of gait disturbance, but his neurological symptoms persisted and intensified. The neurological examination performed on admission to our clinic showed no motor weakness, but revealed hyperreflexia in the lower extremities. His pathologic reflexes, such as the Babinski reflex and Hoffman sign, were also positive bilaterally. He had no voiding difficulty or erectile dysfunction. A brain MRI was unremarkable, but a cervical MRI showed mild cord atrophy without enhancement (Fig. 1A). The somatosensory evoked potentials (SEP) revealed a significantly increased interpeak latency in both the median and tibial SEP systems. The serologic and Cerebrospinal fluid analyses of immunoglobulin M, immunoglobulin G, and polymerase chain reaction (PCR) for varicella zoster virus, cytomegalovirus, herpes simplex virus, and human T-lymphotropic virus 1, were negative. The CD4+ T-cell count was 441.8 cells/μL (500–1600) and the CD4/CD8 T-cell ratio was 0.46 (0.69–1.53). The HIV quantitative PCR test was negative. Considering the clinical, radiological, and serological findings, vacuolar myelopathy was thought to be the cause of the spastic paraparesis. However, an abnormality in VLCFAs was noted. The hexacosanoic acid (C26:0) level was elevated to 1.793 μmol/L (normal, 0–1.31 μmol/L). The hexacosanoic acid/tetracosanoic acid (C24:0/C22:0) ratio and the hexacosanoic acid/docosanoic acid (C26:0/C22:00) ratio were also elevated to 1.952 and 0.080 (normal C24:0/C22:0 ratio, 0–1.39; normal C26:0/C22:0 ratio, 0–0.023), respectively. We genetically analyzed the proband via next-generation sequencing to diagnose ALD. A known pathogenic mutation (c.1876G>A, pAla626Thr hemizygous mutation) was found in the ATP-binding cassette, subfamily D, member 1 (ABCD1) gene (Fig. 1B), and the proband's mother was revealed to be a heterozygous carrier. The patient was finally diagnosed with X-ALD mimicking vacuolar myopathy.

3. Discussion

ALD is an X-linked neurometabolic disorder that affects the central nervous system, adrenal cortex, and testes. It is caused by the ABCD1 gene, which encodes a peroxisomal membrane. This is associated with impaired peroxisomal beta-oxidation and accumulation of VLCFAs, which cause axonopathy with microgliosis with relative sparing of the myelins.[5] Clinically, X-ALD can be divided into Addison only, presymptomatic, adrenomyeloneuropathy (AMN) with cerebral involvement, AMN without cerebral involvement, and spinocerebellar phenotypes according to neuroimaging and clinical findings. Pure AMN usually manifests with spastic paraparesis, sensory disturbance, and urinary incontinence, while AMN patients with cerebral involvement usually show personality changes, visual disturbance, and dysarthria. The spinocerebellar type is rare, constituting 1% to 2% of total ALD cases, and typically shows cerebellar ataxia and dysarthria. Interestingly, this phenotype seems to have ethnic variability: there is a higher prevalence in Asian countries, but further studies are needed to elucidate it.[6] Spine MRIs of X-ALD have a high prevalence of cord atrophy and may also show white matter changes in the cerebral or cerebellar hemisphere; several studies have described the importance of neuroimaging to diagnosis of the disease.[5,7] Other studies have also emphasized the SEP abnormalities that are frequently seen in X-ALD.[8]

Vacuolar myelopathy is the most common chronic myelopathy associated with HIV infection. Interestingly, even in vacuolar myopathy, there is a high prevalence of spinal cord atrophy. Rarely, a non-enhancing high-signal area in the cervical or thoracic spinal cord can also be observed; these findings are also a useful imaging marker for the diagnosis of HIV-related vacuolar myelopathy.[1,2] The diagnosis of vacuolar myopathy is based on the exclusion of serologic abnormalities such as opportunistic infections and vitamin B12 deficiencies; less importance is given to VLCFA.[2] It is noteworthy that both X-ALD and HIV-related vacuolar myopathy clinically present with isolated spastic paraparesis. Therefore, additional laboratory workups including VLCFA can be crucial for the differentiation of the 2 diseases in HIV patients. Furthermore, in both vacuolar myelopathy and

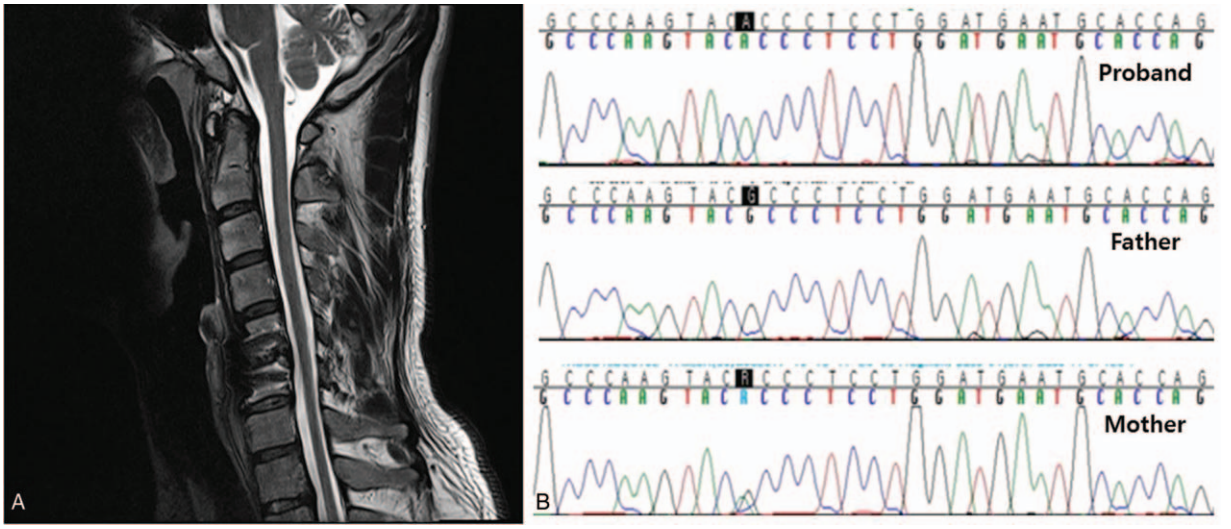

Figure 1. The cervical spine magnetic resonance imaging of the patient shows mild cord atrophy (A). The sanger sequencing of the proband and his family showed a known pathogenic mutation (c.1876G>A, p.A626T) in ABCD1 gene (B). ABCD1 = ATP-binding cassette, subfamily D, member 1.

X-ALD, there is a high prevalence of SEP abnormalities, making the differential diagnosis of the 2 diseases more challenging. The ABCD1 gene, which causes X-ALD, has 2 hot spots: the transmembrane and the nucleotide binding domain. A recent Korean genetic analysis of X-ALD showed a high rate of missense mutation (56%).[9] Our case concurs with these findings, as c.1876G>A is a known pathogenic missense mutation of the nucleotide binding domain.[10] The patient's mother was a carrier. Although carriers are asymptomatic, recent reports describe mild neurological deficits in these carriers that may manifest as sensory ataxia, fecal incontinence, and pain in the fourth or fifth decade of life.[5] In our case, the patient's mother showed no neurological deficits, but time is needed to elucidate them.

We could not completely rule out the patient having both vacuolar myelopathy and X-ALD. However, vacuolar myopathy usually presents in patients with a long duration of HIV, and low CD4 cell counts, unlike our patient.[1] Although rare, isolated spastic paraparesis can occur in HIV patients; additional tests such as VLCFA can be useful for the differential diagnosis. More data are needed to understand the pathological mechanisms underlying the 2 diseases.

Author contributions

Conceptualization: Jin-Sung Park.
Data curation: Jin-Sung Park.
Writing – original draft: Donghwi Park.
Writing – review and editing: Donghwi Park.

References

[1] Anneken K, Fischera M, Evers S, et al. Recurrent vacuolar myopathy in HIV infection. J Infect 2006;52:e181–3.
[2] Chong J, DiRocco A, Tagliati M, et al. MR findings in AIDS-associated myelopathy. AJNR Am J Neuroradiol 1999;20:1412–6.
[3] Fernandez-Fernandez FJ, de la Fuente-Aquado J, Ocampo-Hermida A, et al. Remission of HIV-associated myelopathy after highly active antiretroviral therapy. J Postgrad Med 2004;50:195–6.
[4] Di Ricco A. Disease of the spinal cord in human immunodeficiency virus infection. Semin Neurol 1999;19:151–5.
[5] Engelen M, Kemp S, de Visser M, et al. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow up and management. Orphanet J Rare Dis 2012;7:51.
[6] Takemoto Y, Suzuki Y, Tamakoshi A, et al. Epidemiology of X-linked adrenoleukodystrophy in Japan. J Hum Geent 2002;47:590–3.
[7] Castellano A, Papinutto N, Cadioli M, et al. Quantitative MRI of the spinal cord and brain in adrenomyeloneuropathy: in vivo assessment of structural changes. Brain 2016;139:1735–46.
[8] Restuccia D, Di Lazzaro V, Valeriani M, et al. Abnormalities of somatosensory and motor evoked potentials in adrenomyeloneuropathy: comparison with magnetic resonance imaging and clinical findings. Muscle Nerve 1997;20:1249–57.
[9] Park HJ, Shin HY, Kang HC, et al. Clinical and genetic aspects in twelve Korean patients with adrenomyeloneuropathy. Yonsei Med J 2014;55:676–82.
[10] Wang Y, Busin R, Reeves C, et al. X-linked adrenoleukodystrophy: ABCD1 de novo mutations and mosaicism. Mol Genet Metab 2011;104:160–6.