J Korean Assoc Electrodiagn Med EMG

CASE REPORT
ISSN 1229-6066
http://dx.doi.org/10.18214/jkaem.2016.18.1.28
J Korean Assoc EMG Electrodiagn Med 18(1):28-31, 2016

증례보고: Asp38Ala 돌연변이로 인한 비Val30Met TTR형의 가족성 아밀로이드 다발성신경병증

박천웅, 박은숙, 최자영, 조유나, 나동욱

연세대학교 의과대학 재활의학교실

Case Report: Non-Val30Met TTR Type Familial Amyloid Polyneuropathy with Asp38Ala Mutation

Chunung Park, Eun Sook Park, Ja Young Choi, Yoona Cho, Dong-wook Rha

Department of Rehabilitation Medicine and Research Institute, Yonsei University College of Medicine, Seoul, Korea

There are three precursor proteins of amyloid inducing familial amyloid polyneuropathy (FAP): transthyretin (TTR), Apolipoprotein A-1, and Gelsolin. Abnormal TTR expression is most frequently discovered in FAP and the genotypes are correlated with clinical features. Since the substitution of methionine for valine at position 30 is most common gene mutation, TTR type FAP is divided into Val30Met type FAP and non-Val30Met type FAP. Asp38Ala mutation found in non-Val30Met type FAP usually accompanied the autonomic symptoms and only reported in male persons in Korea. We reported the clinical characteristics and disease progression of first Korean female person with Asp38Ala mutation who didn't show autonomic symptoms.

Key Words: amyloid neuropathies, transthyretin-related amyloid fibril protein

Introduction

Familial amyloid polyneuropathy (FAP) is one form of hereditary amyloidosis, initially showing polyneuropathy and autonomic dysfunction but later involving many visceral organs. This disorder was first clearly described in Portugal in 1952.[1] The understanding of FAP, including the molecular pathogenesis and diagnostic technology, has greatly progressed. There are three main types of FAP, defined according to the precursor protein of amyloid: transthyretin (TTR), apolipoprotein A-1, and gelsolin.[2] TTR is a main constituent of amyloid deposits in FAP,[3] and the complete amino acid sequence of TTR-related amyloid fibril protein was reported in 1983, showing one amino acid substitution (a valine-to-methionine change at position 30).[4] With use of DNA analysis or protein chemistry techniques, more than 80 mutations

Received April 4, 2016
Revised (1st) May 10, 2016, (2nd) June 2, 2016
Accepted June 2, 2016
Corresponding Author: Dong-wook Rha
Department of Rehabilitation Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: 82-2-2228-3717, Fax: 82-2-363-2795, E-mail: medicus@yuhs.ac

have been identified as causative gene abnormality in TTR type FAP. TTR type FAP is classified into Val30Met type FAP and non-Val30Met type FAP because the substitution of methionine for valine at position 30 (Val30Met) is the most common and showing clinical similarities.[5,6] Contrarily, non-Val30Met type FAP is less common and its clinical features are various according to the type of genetic mutations.[7] It has been reported that various genotypes, such as Ala25Tyr and Asp18Gly, are associated with specific phenotypes. However, phenotype of Asp38Ala mutation has been reported mainly in male patients and even never in Korean female patients.

We report a first female case of non-Val30Met type FAP with Asp38Ala mutation in Korea and describe her detailed clinical features, not accompanied with autonomic symptoms.

Case Report

A 57-year-old female, who was diagnosed with hypertrophic cardiomyopathy (HCMP) 2 years ago, underwent sustained ventricular tachycardia without improvement by cardioversion, and admitted to cardiology department. Fabry disease was suspicious on cardiac echo and magnetic resonance imaging, but gene study for Fabry disease was negative. She was diagnosed with cardiac amyloidosis by muscle biopsy (Fig. 1) and discharged after insertion of implantable cardioverter defibrillator (ICD).

After discharge, she was consulted to rehabilitation department to evaluate her tingling sensation and sensory impairments in both arms and legs since 3 years ago. Tingling sensation started with discomfort in the feet and sensory loss has progressed above both ankle 6 months after onset. Tingling sensations and sensory loss gradually extended to the knees and both upper extremities started from both hands. She felt tingling sensations and sensory loss at bilateral 1st to 3rd fingers. She was diagnosed with bilateral carpal tunnel syndrome based on electrodiagnostic examination, but did not improve after operation about 2 years ago. She had no autonomic dysfunction such as orthostatic hypotension, constipation and diarrhea.

On her family history, her mother died from cardiac arrhythmia, her brother diagnosed myocardial hypertrophy and her sister suffered from tingling sensation in both hands. On physical examination, muscular strengths of the ankle plantar flexor were reduced to the fair grade and sensory examination was also impaired below knee.

A sensory nerve conduction study showed no response and low amplitude of sensory nerve action potentials at both upper and lower extremities. A motor nerve conduction study showed slow conduction velocity, no response and low amplitudes of compound muscle action potential at both upper and lower extremities. On needle electromyography, positive sharp waves were observed in the both paraspinal muscles, both upper and lower extremities.

We diagnosed her with peripheral sensory motor polyneuropathy accompanying axonal involvements at both upper and lower extremities, combined with carpal tunnel syndrome. According to these findings, we suspected FAP and referred her for genetic evaluation. Non-Val30Met type FAP with Asp38Ala mutation was confirmed (Fig. 2), and same Asp38Ala

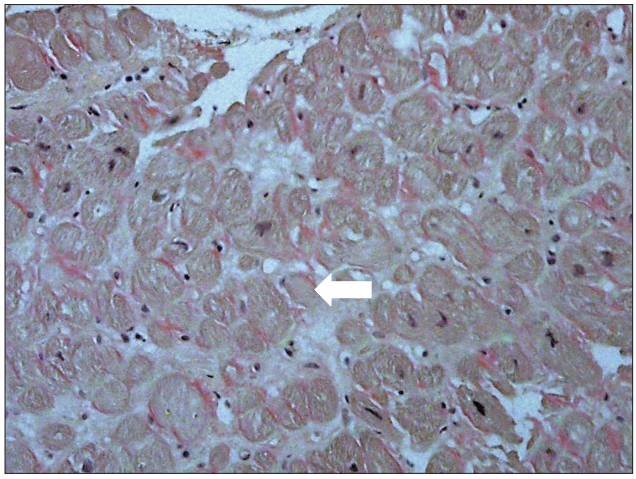

Fig. 1. Congo red stained specimen of cardiac muscle. Amyloid is presented as amorphous whitish materials (arrow) under light microscopy(×200).

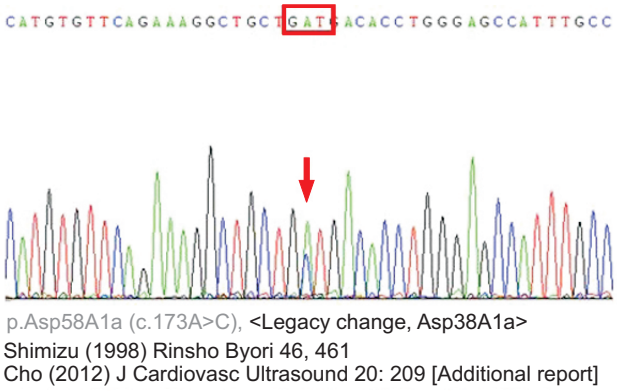

Fig. 2. Sequencing from DNA of exon of TTR gene. Asp38Ala substitution is noted.

mutation was found in her brother.

Discussion

Amyloid can infiltrate to organ, vessel, cardiac muscles and connective tissues. If amyloid infiltrate to peripheral nervous system, it shows polyneuropathy symptoms.[7] FAP's symptoms usually start with discomfort in the feet, including numbness and pain. A few months after onset, sensory loss has progressed above the ankle level and motor deficits develop in the feet and lower legs as well. During the following months and years, the sensory deficit gradually extends to the thighs and then to the upper extremities. The motor deficits also follow a length-dependent progression, and walking without an aid is getting difficult.[2]

FAP, caused by deposit of mutated TTR, was classified into two types, type I (portuguese) and II (Indiana/swiss) according to the geographical distribution and clinical signs. However, recent genetic analysis elucidated that type I is mostly caused by Val30Met mutation, and type II is caused by relatively rare mutations such as His58, Ser84, Asp70 of non-Val30Met type. As more mutations were found by genetic analysis, it was known that phenotypes are correlated with genotypes. Val30Met type FAP, previously known as type I, shows autonomic dysfunction and polyneuropathy from the beginning, but non-Val30Met type FAP shows various clinical signs and symptoms according to kind of genetic mutation.[7]

Non-Val30Met type FAP caused by Asp38Ala substitution has been reported rarely and only 8 cases were reported in Korea.[8-10] They were all male patients and accompanied with autonomic dysfunctions without exception such as orthostatic hypotension, diarrhea, impotence, and urinary incontinence. Three female patients with Asp38Ala substitution type FAP were reported in Japan and all of them suffered from autonomic dysfunctions such as dizziness, constipation and diarrhea.[11-13] On the contrary, this patient, the first female case of Asp38Ala substitution type FAP reported in Korea, experienced relatively early-onset cardiomyopathy without autonomic symptoms. However, she had common clinical features with previously reported male patients; cardiac involvement, and electrodiagnostic abnormalities showing sensory motor polyneuropathy or other compressive focal neuropathy. Although autonomic dysfunctions are known to be less in non-Val30Met type FAP compared to Val30Met type FAP, all previously reported cases suffered from autonomic symptoms whether they were male or female. It was unclear whether this case is exceptional or ethnic difference affected the phenotypes. Further collection of Korean female cases may determine whether ethnicity may affect the clinical characteristics of Asp38Ala substitution type FAP.

References

1. Andrade C: A peculiar form of peripheral neuropathy. Brain 1952: 75(3): 408-27
2. Planté-Bordeneuve V, Said G: Familial amyloid polyneuropathy. Lancet Neurol 2011: 10(12): 1086-97
3. Costa PP, Figueira AS, Bravo FR: Amyloid fibril protein related to prealbumin in familial amyloidotic polyneuropathy. Proc Natl Acad Sci U S A 1978: 75(9): 4499-503
4. Tawara S, Araki S, Toshimori K, Nakagawa H, Ohtaki S: Amyloid fibril protein in type I familial amyloidotic polyneuropathy in Japanese. J Lab Clin Med 1981: 98(6): 811-22.7
5. Connors LH, Richardson AM, Theberge R, Costello CE: Sequence Communication: Tabulation of transthyretin (TTR)

variants as of 1/1/2000. Amyloid 2000: 7(1): 54-69
6. Koike H, Ando Y, Ueda M, Kawagashira Y, Iijima M, Fujitake J, et al: Distinct characteristics of amyloid deposits in early- and late-onset transthyretin Val30Met familial amyloid polyneuropathy. J Neurol Sci 2009: 287(1): 178-84
7. Ikeda S-i, Nakazato M, Ando Y, Sobue G: Familial transthyretin-type amyloid polyneuropathy in Japan Clinical and genetic heterogeneity. Neurology 2002: 58(7): 1001-7
8. Jang M, Lee GY, Kim K, Kim SJ, Kim JS, Lee SY, et al: Asp58Ala is the Predominant Mutation of the TTR Gene in Korean Patients with Hereditary Transthyretin-Related Amyloidosis. Ann Hum Genet 2015: 79(2): 99-107
9. Cho HJ, Yoon JY, Bae MH, Lee JH, Yang DH, Park HS, et al: Familial transthyretin amyloidosis with variant Asp38Ala presenting with orthostatic hypotension and chronic diarrhea. J Cardiovasc Ultrasound 2012: 20(4): 209-12
10. Kim YJ, Lee J, Park J, Kim S, Jung I, Lim HJ, et al: Familial Amyloidotic Polyneuropathy With Transthyretin Gene Mutation. J Korean Neurol Assoc 2011: 29(3): 220-3
11. Kishikawa M, Nakanishi T, Miyazaki A, Shimizu A, Kusaka H, Fukui M, et al: A new amyloidogenic transthyretin variant,[D38A], detected by electrospray ionization/mass spectrometry. Amyloid 1999: 6(4): 278-81
12. Tachibana N, Tokuda T, Yoshida K, Taketomi T, Nakazato M, Li Y-F, et al: Usefulness of MALDUTOF mass spectrometry of immunoprecipitated serum variant transthyretin in the diagnosis of familial amyloid polyneuropathy. Amyloid 1999: 6(4): 282-8
13. Yazaki M, Takei Y-I, Katoh M, Ikeda S-I: Postmortem findings in two familial amyloidosis patients with transthyretin variant Asp38Ala. Amyloid 2000: 7(4): 270-7