JCN Open Access LETTER TO THE EDITOR

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2020;16(4):704-706 / https://doi.org/10.3988/jcn.2020.16.4.704

Ultrasonography Findings in Hereditary Neuropathy with Liability to Pressure Palsies Due to Single-Nucleotide Substitution

Yong Kyun Kim[a]
Suho Ro[a]
Yun Hyeong Jeong[a]
Soei Ann[a]
Hyung Jun Park[b]
Bum Chun Suh[a]

[a]Department of Neurology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea
[b]Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Dear Editor,

Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant demyelinating neuropathy characterized by recurrent entrapment neuropathies such as ulnar and peroneal nerve palsy. Its prevalence has been estimated at 7−16 per 100,000 people.[1] Most cases are caused by the deletion of *PMP22* at chromosome 17p11.2−p12, and rarely also by a point mutation within the gene.[2-4] Here we report ultrasonography and genetic findings in an HNPP patient with a novel point mutation in *PMP22*.

A 27-year-old man visited our clinic due to right-arm weakness that recurred 2 weeks earlier while carrying a heavy object. The patient had suffered the same symptom 5-years previously, but otherwise had no known underlying disease. A neurologic examination revealed MRC grade IV weakening of the extensor of the right wrist and metacarpophalangeal joint. A nerve conduction study (NCS) showed a conduction block in the right radial nerve. Generalized prolongations of terminal latency and F-wave latency were observed. The NCS findings for the patient's median and ulnar nerves were similar to those seen in carpal tunnel and cubital tunnel syndrome. Ultrasonography examinations of the cervical root and nerves of the upper and lower extremities revealed enlargement only in the median and ulnar nerves at the wrist and at the elbow, respectively (Fig. 1). The NCS and ultrasonography results obtained 5-years previously were the same except for the absence of radial nerve conduction block.

The patient was clinically diagnosed with HNPP. However, the deletion of *PMP22* had not been detected in the multiplex ligation–dependent probe amplification assay performed 5 years previously, and so we performed next-generation sequencing to identify any pathogenic variant. A null variant (NM_000304.3: c.79-2A>C) in the *PMP22* was detected, which was confirmed by Sanger's sequencing. We regarded this as a pathogenic variant causing HNPP and so diagnosed him with HNPP. The patient fully recovered after 3 months of rest.

Most (84%) HNPP patients exhibit *PMP22* deletion,[5] but a point mutation within the gene can also cause this condition.[2-4] The c.79-2A>C variant identified in the present study is a novel variant. However, we were able to classify this variant as pathogenic based on the following evidence: 1) it is a null variant in a gene with loss-of-function mechanism, 2) it is not included in the controls in the Genome Aggregation Database (http://gnomad.broadinstitute.org), 3) multiple lines of computational evidence support a deleterious effect of the gene, and 4) the patient's phenotype was highly specific for a disease with a single genetic etiology.[6] Additionally, the c.79-2A>G variant—which is a different nucleotide change at the same position—was previously reported as a pathogenic variant associated with HNPP.[2]

The swelling of peripheral nerves at common entrapment sites has been reported in HNPP—the median nerve at the wrist and ulnar nerve at the elbow—even without symp-

Received April 21, 2020
Revised June 10, 2020
Accepted June 10, 2020

Correspondence
Bum Chun Suh, MD, PhD
Department of Neurology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine,
29 Saemunan-ro, Jongno-gu, Seoul 03181, Korea
Tel +82-2-2001-2101
Fax +82-2-2001-1938
E-mail bcsuh@skku.edu

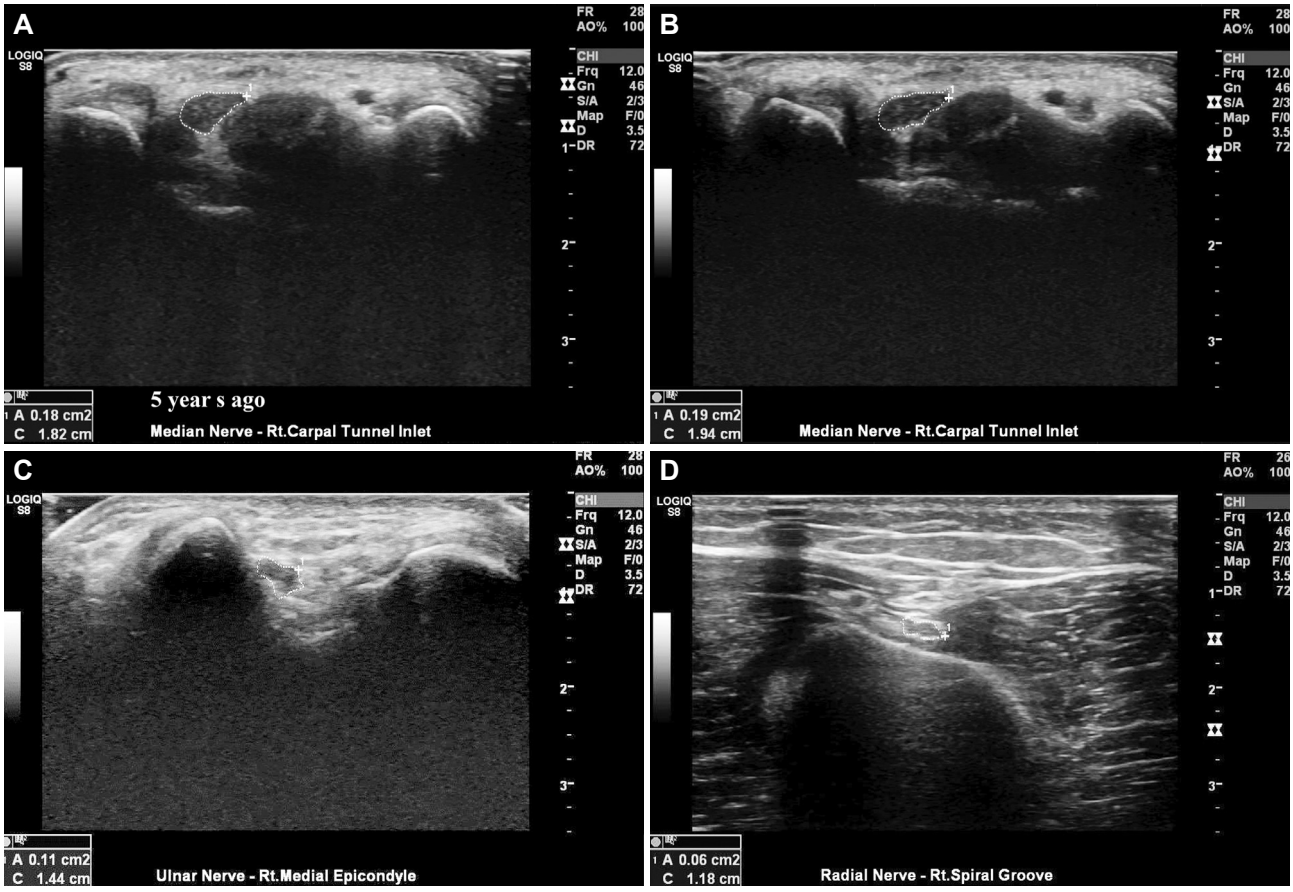

Fig. 1. Ultrasonography findings of hereditary neuropathy with liability to pressure palsies with a novel point mutation. Ultrasonography revealed swelling of peripheral nerves at common entrapment sites: —the median nerve at the wrist (A and B) and the ulnar nerve at the elbow (C). The radial nerve did not show any nerve enlargement at the compression site (D). These findings did not differ from those in nerve ultrasonography performed 5 years previously (A and B).

toms,[7] but to the best of our knowledge this feature was in subjects with *PMP22* deletion. Notably, our patient also had swelling of the median nerve at the wrist and the ulnar nerve at the elbow that had not changed over 5 years in the absence of other sites with nerve enlargement. The radial nerve was carefully inspected using ultrasonography at the upper arm as well, but this did not reveal swelling, which was also the case in ultrasonography performed 5-years previously. However, we could not exclude the possibility of the restoration of the radial nerve swelling, because we performed ultrasonography at 2 months after symptom onset.

This case allows us to infer that the ultrasonography findings of HNPP with a c.79-2A>G variant are not distinct from a *PMP22* deletion, and that ultrasonography should mainly show chronic nerve enlargement at common entrapment sites, regardless of the location of acute symptom.

Author Contributions

Conceptualization: Bum Chun Suh, Yong Kyun Kim. Data curation: Yong Kyun Kim. Formal analysis: Yong Kyun Kim. Investigation: Bum Chun Suh, Yong Kyun Kim. Methodology: Bum Chun Suh. Project administration: Bum Chun Suh. Resources: Bum Chun Suh. Supervision: Bum Chun Suh. Validation: Bum Chun Suh, Hyung Jun Park. Visualization: Bum Chun Suh, Yong Kyun Kim. Writing—original draft: Yong Kyun Kim. Writing—review & editing: Hyung Jun Park, Suho Ro, Yun Hyeong Jeong, Soei Ann.

ORCID iDs

Yong Kyun Kim https://orcid.org/0000-0002-8666-2405
Suho Ro https://orcid.org/0000-0003-3378-561X
Yun Hyeong Jeong https://orcid.org/0000-0001-5277-3978
Soei Ann https://orcid.org/0000-0003-2744-5651
Hyung Jun Park https://orcid.org/0000-0003-4165-8901
Bum Chun Suh https://orcid.org/0000-0002-3947-5615

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

REFERENCES

1. van Paassen BW, van der Kooi AJ, van Spaendonck-Zwarts KY, Verhamme C, Baas F, de Visser M. PMP22 related neuropathies: Charcot-Marie-Tooth disease type 1A and hereditary neuropathy with liability to pressure palsies. *Orphanet J Rare Dis* 2014;9:38.
2. Koutsis G, Pandraud A, Polke JM, Wood NW, Panas M, Karadima G, et al. Novel peripheral myelin protein 22 (PMP22) micromutations as-

sociated with variable phenotypes in Greek patients with Charcot-Marie-Tooth disease. *Brain* 2012;135(Pt 8):e217.
3. Fusco C, Spagnoli C, Salerno GG, Pavlidis E, Frattini D, Pisani F. Hereditary neuropathy with liability to pressure palsy (HNPP): report of a family with a new point mutation in PMP22 gene. *Ital J Pediatr* 2017;43:97.
4. Liao YC, Tsai PC, Lin TS, Hsiao CT, Chao NC, Lin KP, et al. Clinical and molecular characterization of PMP22 point mutations in Taiwanese patients with inherited neuropathy. *Sci Rep* 2017;7:15363.
5. Nelis E, Van Broeckhoven C, De Jonghe P, Löfgren A, Vandenberghe A, Latour P, et al. Estimation of the mutation frequencies in Charcot-Marie-Tooth disease type 1 and hereditary neuropathy with liability to pressure palsies: a European collaborative study. *Eur J Hum Genet* 1996;4:25-33.
6. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17:405-424.
7. Ginanneschi F, Filippou G, Giannini F, Carluccio MA, Adinolfi A, Frediani B, et al. Sonographic and electrodiagnostic features of hereditary neuropathy with liability to pressure palsies. *J Peripher Nerv Syst* 2012;17:391-398.