Movement Disorders
CLINICAL PRACTICE
LETTERS: GENOTYPE AND PHENOTYPE

Neuronal Intranuclear Inclusion Disease Presenting with Voice Tremor

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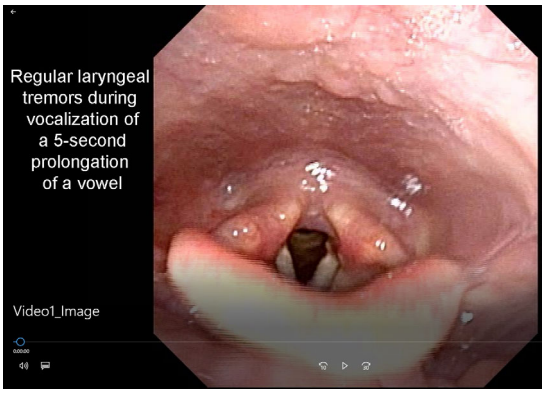
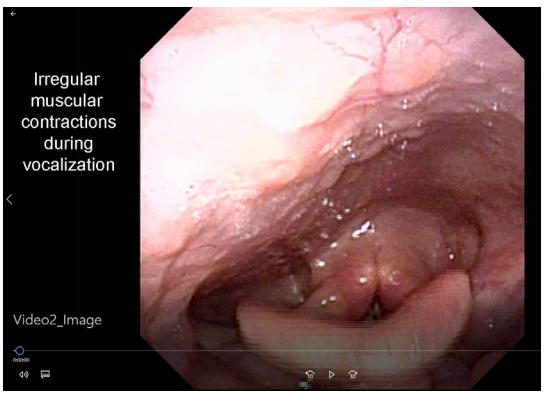
Neuronal intranuclear inclusion disease (NIID) is an inherited neurodegenerative disease caused by an abnormal GGC repeat expansion of the *NOTCH2NCL* gene and characterized by eosinophilic hyaline intranuclear inclusions seen in neurons, skin cells, fibroblasts, and skeletal muscle cells.[1,2] Brain magnetic resonance imaging (MRI) shows characteristic hyperintense areas in the corticomedullary junction on diffusion-weighted imaging (DWI). Based on the initial and main symptoms, NIID-affected subjects were classified as dementia-dominant or limb weakness-dominant phenotype.[2] However, an abnormal GGC repeat expansion of *the NOTCH2NCL* gene has also been reported in hereditary essential tremor-6 (ETM6).[3] ETM6 is characterized by adult-onset kinetic and/or postural tremor in the upper limbs without associated cognitive impairments nor weakness. Skin biopsy shows intranuclear eosinophilic inclusions in the fibroblasts and sweat gland cells; their brain MRI also lack characteristic hyperintense areas in the corticomedullary junction on DWI. Therefore, NIID is considered a heterogeneous disorder, and patients may present with an essential tremor before the onset of other symptoms. Here, we report a case of NIID with voice tremor without associated dementia or muscle weakness.

A 55-year-old woman with a 2-year history of difficulty speaking presented to our hospital. The patient's mother was clinically diagnosed with Alzheimer's disease. A strained and strangled voice was observed in the patient. She showed a slight "no-no head tremor" without rigidity and bradykinesia and no



Video 1. Laryngoscopy revealed regular laryngeal tremors only during vocalization of a 5-second prolongation of a vowel, such as "ee".
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13382



Video 2. Laryngoscopy revealed irregular muscular contractions from the larynx to the entire of the pharynx and intermittent opening of the vocal cords during vocalization.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13382

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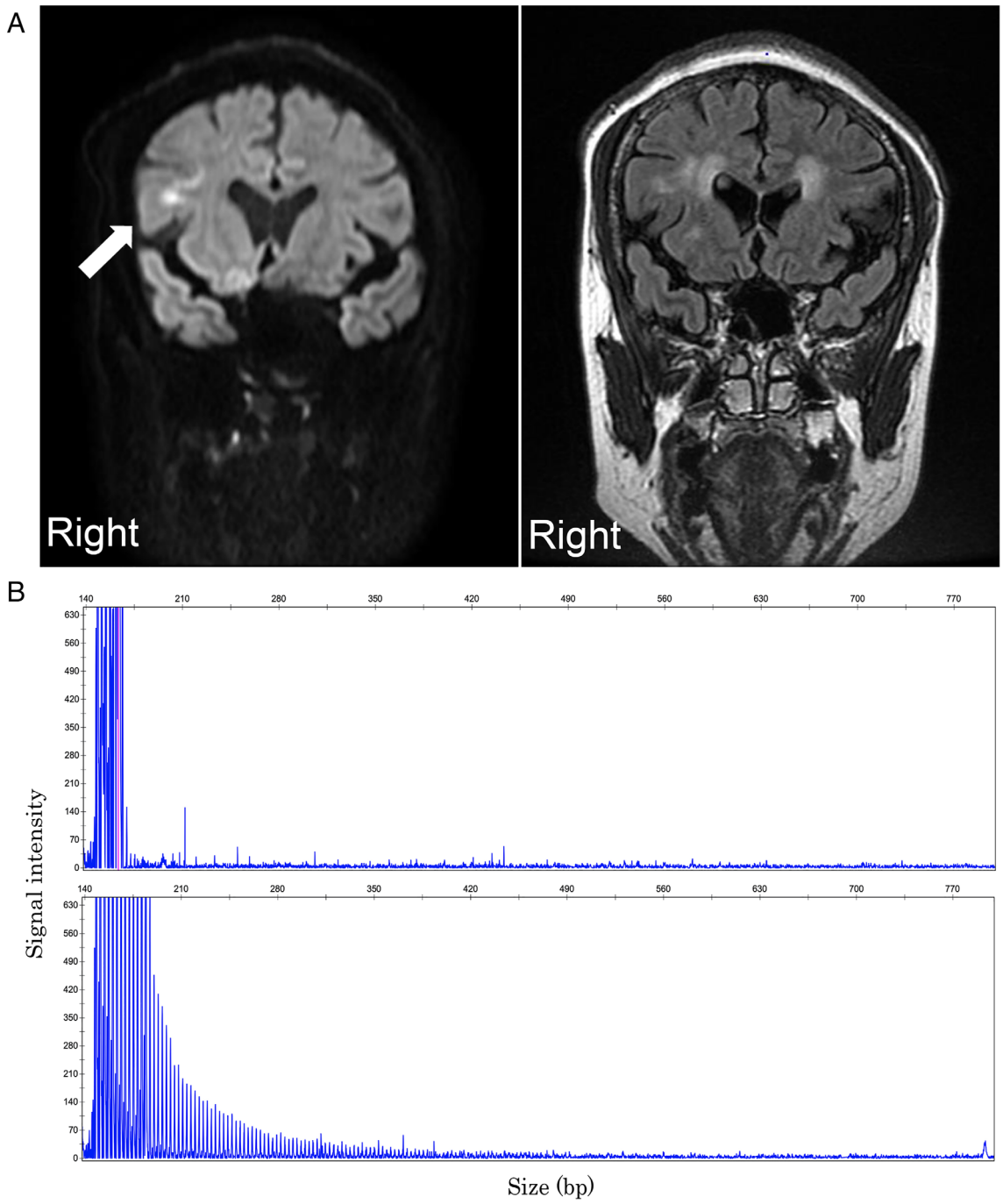

FIG 1. MRI and genetic study of the current patient. (**A**) Brain MRI. Coronal sections of diffusion-weighted imaging (DWI, left panel) and fluid-attenuated inversion recovery images (FLAIR, right panel). The arrow indicates a subcortical hyperintense lesion located at the right inferior frontal subcortex on DWI. (**B**) These are representative results of repeat-primed PCR analysis showing GGC repeat expansions in the *NOTCH2NLC* gene. In unaffected individuals, no GGC repeat expansions are detected (top panel). In this patient, a typical sawtooth tail pattern caused by a GGC repeat expansion in the *NOTCH2NLC* gene was detected (bottom panel). *bp, Base pair.

pyramidal signs. She could not maintain the Mann's posture and could not perform tandem gait walking, exhibiting balance problems. She had no limb ataxia nor dysarthria. Her Mini-Mental State Examination score was 27, and her frontal assessment battery score was 18. Her trail making test parts A and B took 67 and 138 seconds, respectively, indicating no decline in her attention, alertness, nor executive function. The standard language test results for aphasia were normal. It was observed that

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the values obtained from the sustained vowels /a/ by the Multi-Dimensional Voice Program (KayPentax, NJ) were compatible with voice tremor (noise-to-harmonic ratio, 0.190; amplitude tremor intensity index, 23.4%; degree of voice breaks, 25.0%). Laryngoscopy revealed regular laryngeal tremors only during vocalization of a 5-second prolongation of a vowel, such as "ee" (Video 1). Moreover, laryngoscopy revealed irregular muscular contractions from the larynx to the entire of the pharynx and intermittent opening of the vocal cords during vocalization (Video 2). Her voice sounded strained or strangled with intermittent interruptions. Thus, we diagnosed the patient with voice tremor. Her brain MRI showed extensive hyperintensities in the bilateral cerebral white matter on fluid-attenuated inversion recovery images. Hyperintensities in the corticomedullary junction of the right inferior frontal and left parietal regions were also observed (Fig. 1A). A skin biopsy revealed nuclear inclusions, positive for anti-p62 antibody, in adipocytes and glandular cells. Additionally, a few inclusions were noted in fibroblasts and peripheral nerve bundles. Written informed consent for genetic diagnosis was then obtained from the patient. This study was approved by the institutional review board committees of Niigata University (#G2015-0849). Abnormal expansion of GGC repeats in the 5′UTR of the *NOTCH2NCL* gene was detected using repeat-primed PCR (Fig. 1B).[1] The long-range PCR analysis revealed that the expanded allele contains 89 GGC repeats. We were unfortunately unable to test her mother.

The patient showed voice tremor, head tremor, and truncal ataxia without any associated dementia nor limb weakness. The clinical presentation corresponded to ETM6, but not to NIID.[3] Some patients with ETM6 may present with tremors in the head and abnormal phonation. In addition, brain MRI in ETM6 patients show no leukoencephalopathy. Moreover, patients with essential tremor due to GGC repeat expansion reveal no brain MRI abnormalities over 10 years.[4] Therefore, MRI findings in this patient were compatible with NIID, but not ETM6. The imaging features of this patient were typical and did not correspond to the classic definition of NIID.

We consider that cerebellar dysfunction may be responsible for the voice tremor in our patient, as several patients diagnosed with essential tremors may display very subtle cerebellar signs on neurological examination.[5] Abnormal GGC repeat expansion of the *NOTCH2NCL* gene may cause variable neurological symptoms because of this gene expression throughout the nervous system. Thus, we suggest that voice tremor might be an additional clinical symptom of NIID and the *NOTCH2NLC* gene-related repeat expansion disorder.

Author Roles

(1) Project: A. Conception, B. Organization, C. Execution; (2) Manuscript Preparation: A. Writing the First Draft, B. Review and Critique; (3) Manuscript: A. Revising for intellectual content, B. Approval of the final version for publication.

T.T.: 1B, 1C; 2A; 3A, 3B
M.K.: 1A, 1B, 1C; 2B; 3A, 3B
Y.H.: 1A, 1B, 1C; 3A, 3B
H.B.: 1A, 1C; 2B; 3A, 3B
A.I.: 1B, 1C; 2B; 3A, 3B
M.U.: 1B, 1C; 2B; 3A, 3B
T.K.: 1B, 1C; 2B; 3A, 3B
A.H.: 1C; 2B; 3A, 3B
T.I.: 1C; 2B; 3A, 3B
O.O.: 1C; 2B; 3A, 3B

Disclosures

Ethical Compliance Statement: The study was approved by the Ethical Committee of the institutions concerned and the patient agreed with the publication after receiving all information relevant to the study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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