DND Dementia and Neurocognitia Disorder

Letter to the Editor

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Novel Pathogenic Missense *NF1*-Variant Associated With Cognitive Impairment

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Dear Editor,

Early-onset dementia (EOD) is a clinically heterogenous disorder, accounting for 1%–2% of all dementia cases, before 65 years of age.[1] Genetic factors play a crucial role. About 16%–30% cases can be diagnosed with whole exome sequencing.[2] The unique ancestry and genetic makeup of South Asians make it challenging to understand novel variants. The *NF1* gene, which encodes neurofibromin protein, is the main cause of dominantly inherited neurofibromatosis type 1 (NF1).[3] Cognitive deficits can occur throughout the lifespan.[4] The frequency and cognitive phenotype associated with *NF1* the variant are not well understood yet due to early mortality linked to the variant. Herein, we describe and highlight unusual clinical and imaging characteristics of a patient with dementia having a variant of *NF1*.

A 50-year-old right-handed woman presented to our clinic with 18 months of behavioral disturbances including apathy, social withdrawal, lack of personal hygiene, and emotional lability. Subsequently, she developed difficulty in dressing and handling finances. Within 6 months of her first visit, her speech became worse. She became completely dependent for daily activities. Her medical history was notable for an episode of sudden onset giddiness without any loss of consciousness lasting 5 minutes 2 years ago. There was no family history of similar illness or any psychiatric, motor, or memory problems (**Fig. 1**). Systemic examination was unremarkable. Her Addenbrooke's Cognitive Examination III score was 56/100 (normal ≥87/100). Her individual cognitive domain scores were: attention, 10/18; memory, 16/26; fluency, 6/14; language, 20/26; and visuospatial, 4/16. Her cognitive profile showed impaired attention, reduced spontaneous speech, impaired phonemic fluency, and visuo-construction skills (**Fig. 1**). Her lower limbs (right > left), brisk reflexes, extensor planters, and elicitable primitive reflexes showed asymmetric rigidity.

Laboratory investigations to rule out treatable cause of dementia were normal. Brain magnetic resonance imaging (MRI) (**Fig. 1**) showed multiple lacunar infarcts and microbleeds, with T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities in bilateral basal ganglia, thalami, and subcortical locations of bilateral cerebral hemispheres and cerebellum. 18-Fluorodeoxyglucose positron emission tomography MRI brain provided further evidence of hypometabolism in basal ganglia, thalami, and right frontoparietal regions. As the patient was diagnosed to have EOD, genetic analysis in form of whole exome sequencing was performed. A novel pathogenic missense variant in exon 45 of NF1 gene at
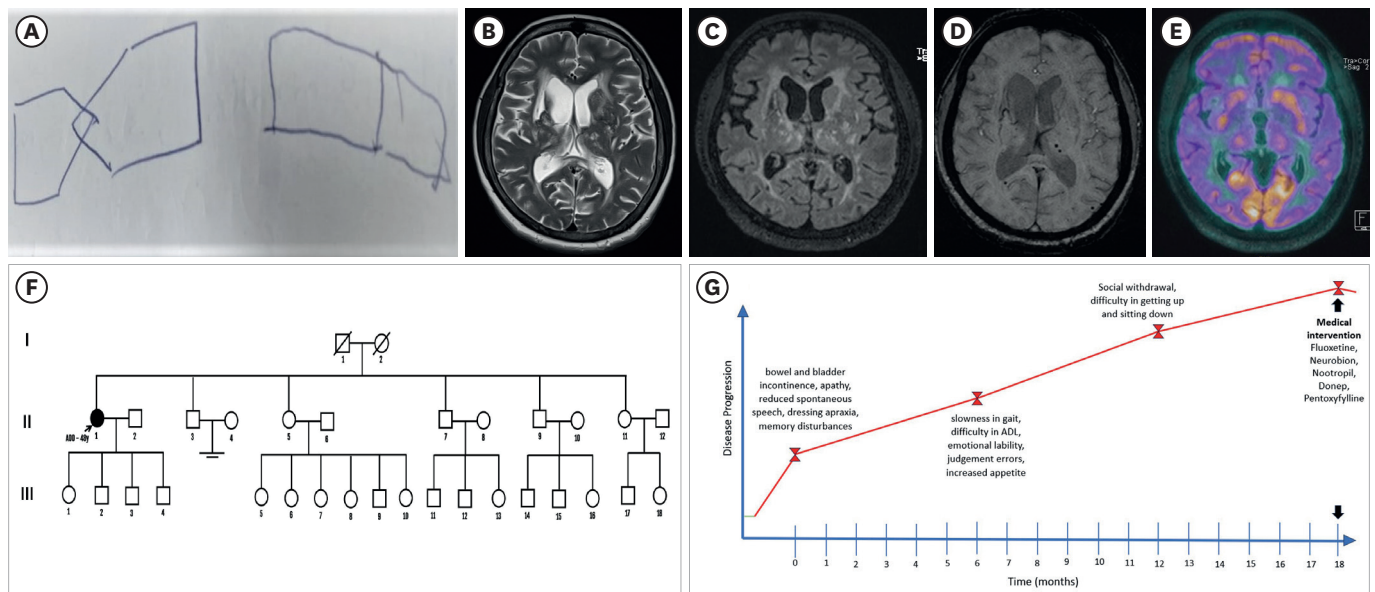
Fig. 1. (A) Impaired visuoconstruction ability in copying intersecting pentagons. (B, C) Brain magnetic resonance imaging axial T2 and fluid-attenuated inversion recovery sequence showing bilateral lacunar infarcts in the basal ganglia and thalamus with periventricular small vessel ischemic changes. (D) Susceptibility weighted image sequence showing evidence of blooming in left thalamus. (E) ^{18}F-fluoro-deoxy glucose positron emission tomography image showing diffuse evidence of diffuse hypometabolism predominantly involving bilateral temporo-parietal regions. (F) Detailed pedigree chart of the family with the proband. (G) Clinical course of the patient from onset to presentation.

Author Contributions

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position c.6764A>C (p.Glu2255Ala) in a heterozygous state was identified. The variant has a low rate of benign missense variation. It is predicted to be a damaging variant by both SIFT and polyPhen2. Based on these, this variant was classified as likely pathogenic per the American College of Medical Genetics and Genomics recommendations.[5] The patient was diagnosed with vascular cognitive impairment associated with pathogenic *NF1* variant. She is managed with symptomatic medications and cognitive stimulation therapy. Only one patient among 105 patients diagnosed with dementia in our Cognitive Disorders Clinic who underwent whole exome sequencing showed this *NF1* variant.

The *NF1* gene is a negative regulator for RAS signaling. It has variable expressivity, penetrance, and mosaicism, making it difficult to diagnose, especially for those without a family history. Possible explanations include *NF1* gene heterogeneity, modifiers, epigenetic regulators, and environment factors like hormones and vitamin D.[6] It primarily affects the peripheral nervous system, the central nervous system, the skin, the skeletal system, and the vascular systems.[3] Children are more often affected by neurofibromatosis than adults. They experience cognitive and behavior problems, including impaired general cognition, attention, reasoning, abstract knowledge, visuo-constructive skills and language disturbances, especially poor reading skills.[7] Deficits in executive function and auditory long-term memory have also been reported.[8] Visuospatial skills are considered hallmark deficits in patients with NF1,[8] while very little is known about auditory memory functions of such patients.

The association between NF1 and dementia has not been confirmed. However, a Finnish cohort has found an increased risk for dementia among individuals with NF1 compared to controls.[3] This is attributed to mosaicism, highlighting the phenotypic heterogeneity observed in patients with *NF1* variants. Brain imaging revealed that our patient might have an *NF1* variant-related vascular disease, which could cause aneurysms. Microaneurysms are formed in the deep grey matter due to lacunar infarcts. Neuroimaging studies of NF1

patients have observed specific findings such as unidentified bright objects (UBOs), which are hyperintensities on T2-weighted or FLAIR without mass effect or contrast enhancement. These were seen in 70% of NF1 patients. They could be diffuse or discrete.[9] However, no robust link has been found between major cognitive deficits in NF1 and UBOs.

Reverse phenotyping is crucial for identifying rare pathogenic variants as seen in our patient with dementia. Identification of such variants will potentially lead to the development of personalized therapeutic interventions. Genome editing technology holds significant potential for innovative and transformative treatments. However, existing research is insufficient to fully comprehend the roles of genotypes, phenotypes, and genetic heterogeneity in patients with dementia with *NF1* variant. Further research studies with functional studies and advanced imaging are required to better understand novel mechanisms and neural basis of patients with dementia with *NF1* variant.

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