Nasu–Hakola Disease – A Rare Type of Presenile Dementia

Sir,

Nasu–Hakola disease (NHD)—also known as polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL)—is a rare autosomal recessive disorder characterized by progressive presenile dementia and bone cysts caused by mutations in the genes TREM2 and TYROBP. We report the second case of Nasu–Hakola disease from the Indian subcontinent.

A 39-year-old male who is a plumber by occupation presented with gradually progressive behavioral changes for 4 years, bilateral upper limb tremors for 3 years, and recurrent generalized tonic-clonic seizures for 1 year. He had excessive talkativeness, used to repeatedly talk about the same things, inappropriate answers to questions, over-familiarity with strangers, impulsive behavior, difficulty in memorizing recent events, easy distractibility, anger outbursts, and episodes of wandering. There was no history of difficulty in identifying familiar faces, money handling problems, and visuospatial disorientation. One year following the behavioral changes, he developed tremors in both hands while holding a glass and during writing. He had three episodes of generalized tonic-clonic seizures during the last year. He was born as the second child of a non-consanguineous union by vaginal delivery at term without complications. His siblings (one elder brother and a younger sister) and parents (father and mother) had no history of early-onset dementia, movement disorders, seizures, or any other neuropsychiatric manifestations. He was conscious, oriented, had recent memory loss with intact immediate and remote memory, and the Mini-Mental State Examination score was 13/30. He had brisk deep tendon reflexes with bilateral flexor plantar and had primitive reflexes (glabellar tap, palmo Mental, suckling, and grasp reflex). No other neuropsychological assessment of the patient was performed.

Biochemical parameters including electrolytes, renal function, liver function, and blood counts were normal. Non-contrast computed tomography scan of the brain showed bilateral basal ganglia calcification. Magnetic resonance imaging of the brain showed diffuse cerebral atrophy, bilateral basal ganglia hypointensities with diffuse white matter hyperintensities on T2-weighted images [Figure 1a-e]. Cerebrospinal fluid

Figure 1: Non-contrast computed tomography scan of the brain showing bilateral basal ganglia calcification (a), magnetic resonance imaging of the brain showing diffuse cerebral atrophy, bilateral basal ganglia hypointensities, with diffuse white matter hyperintensities on T2-weighted and fluid-attenuated inversion recovery images (b-e), X-ray of hands showing multiple bone cysts (f)
and electroencephalogram were normal. X-ray of hands showed multiple bone cysts [Figure 1f]. The peripheral blood sample was submitted from the patient for genomic DNA extraction after obtaining informed consent. Exome sequencing revealed the presence of c.377T>G mutation (TREM2 gene of Exon 2) in the homozygous state. Genetic tests were not done for the other members of the family. Based on clinical features, imaging findings, and molecular analysis, the patient was diagnosed to have NHD. The family has been counseled that this is a genetic condition with autosomal recessive inheritance. He was treated with antiepileptics and was readmitted 2 months later with status epilepticus following drug default. He developed rhabdomyolysis with acute renal shutdown and severe metabolic acidosis. He was initiated on hemodialysis but unfortunately succumbed to his illness on the third day of admission.

NHD may be the prototype of primary microglial disorders of the nervous system caused by mutations in the TREM2 and TYROBP genes resulting in loss of function of the TREM2-DAP12 immunoreceptor signaling complex. TREM2-DAP12 is required for microglial phagocytosis of neuronal debris and amyloid deposits. In the absence of this complex, microglia become ineffective, amyloid deposits accumulate, and there is myelin loss in the brain. Mutations in the TREM2 or TYROBP gene disrupt normal bone growth due to malfunctioning osteoclasts, which are able to resorb bone tissue less during bone remodeling. Rare genetic variants of the TREM2 gene were found to be associated with an increased risk of other degenerative diseases like Alzheimer’s disease, frontotemporal dementia, amyotrophic lateral sclerosis, and Parkinson’s disease.

The early neurologic stage of NHD, most often in the third or fourth decades of life, is characterized by personality changes of frontotemporal dementia (FTD). Initially, they experience mild memory disturbances and personality changes followed by progressive memory deficits. Generalized seizures are frequently observed. During the later phase, patients progress to profound dementia and become bedridden. The differential diagnosis includes the established forms of familial and nonfamilial frontotemporal dementia. The combination of early-onset FTD with associated seizures and radiographic demonstration of cystic bone lesions is unique and aids in differentiating NHD from other forms of familial and nonfamilial FTD. Our patient presented with early-onset FTD, generalized seizures with bilateral basal ganglia calcification, and had cystic bone lesions which made us consider NHD.

The diagnosis was confirmed by mutational analysis. This case reminds the readers to consider this rare form of dementia in patients presenting with early-onset FTD with seizures. To the best of our knowledge, only one similar case was reported in the literature previously from the Indian subcontinent.

Declaraton of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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