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Clinical and Molecular Study of NPC in Iran: Report of 5 Novel Mutations

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Niemann–Pick disease type C (NPC) is a rare autosomal, recessive, neurovisceral disorder caused by mutations in the NPC1 (95%) or NPC2 (5%) genes. NPC disease has a variable phenotype, whereby an alteration in cholesterol and glycolipid homeostasis leads to a broad spectrum of symptoms that include hepatosplenomegaly, liver dysfunction, and neurological abnormalities such as progressive ataxia, cataplexy, vertical supranuclear gaze palsy, seizures, and impairment of swallowing reflexes. NPC is rarely reported in Iran and during eighteen months ago, 15 patients were diagnosed as NPC by Filipin staining in our department. RT-PCR and sequencing methods were used for molecular investigation for NPC1 and NPC2 genes in 5 patients. All of the five patients (2 female and 3 male) had juvenile form of NPC and had been presented with gait ataxia and so all of them were product of consanguineous marriage too.

Case I: 15 years old boy who had hepatosplenomegaly and jaundice in neonatal period. Liver biopsy at that time was compatible with a lipid storage disease. He had supra vertical gaze palsy in 11 years of age and developed progressive ataxia, dystonia and gelastic cataplexia since two years ago. Brain MRI was normal.

Case II: 3.5 years old boy, splenomegaly was detected at 6 month of age. He had psychomotor developmental delay. He still can't walk, he developed supra vertical gaze palsy and gelastic cataplexia (even when he is in a sitting position) since one years ago. Brain MRI was normal.

Case III. IV: Two sister, aged 13, 17 years old, product of consanguineous marriage; 13 years old sister was presented with chief complaint of progressive ataxia and dysarthria since 9th years of age. Since 11th years of age progressive dysphagia started but now dysphagia is in a plateau state. Cognitive state remains unchanged. She has no seizure nor gelastic cataplexia. There was no history of neonatal jaundice and no splenomegaly was detected. In neurologic examination she had supra vertical gaze palsy. Brain MRI showed nonspecific hypersignal changes in white matter. 17 years old sister had epistaxia at 6th. Year of age and in the work up splenomegaly was detected. Progressive ataxia and dysphagia developed at 7th years of age leading to wheelchair bound state and nasogastric tube feeding at 14 years of age. She died few months ago. Brain MRI showed cerebellar atrophy. In neurologic examination she had supra vertical gaze palsy.

Case V: 13-year-old boy, who presented primarily with neurologic symptoms.

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He started to develop ataxia and dysarthria at the age of eight years. Dementia, dysphagia, and seizures, in that sequence, followed within a couple of years. He was anarthric and bedridden four years after onset. Supranuclear vertical gaze palsy was found at the time of the exam. However, no hepatosplenomegaly or other physical abnormality was noted.

Whole transcribed exons of the NPC1 genes were sequenced and we could find four different unreported homozygous mutations [Case I: (c.1069C>T) p.S357L, Case II: (c.1180C>T) p.Y394H, Case III. IV: (c.1433A>C) p.N 478 T, Case V: (c.1192C>T) p.H398Y]. All of the mutations were software analyzed and were missense mutations.

Keywords: NiemannPick disease types c; Molecular study; Novel mutation