NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

EDITORIAL

Arch Neuropsychiatry 2024;61:99–100
https://doi.org/10.29399/npa.28717

A Potentially Treatable Genetic Disorder Which Presented with Neuropsychiatric Involvement and Drug-Resistant Focal Epilepsy: Niemann-Pick Disease Type C

Ebru ALTINDAĞ[1], Yasemin ALANAY[2], Betul BAYKAN[3], Aysin DERVENT[4]

[1]Istanbul Florence Nightingale Hospital, Department of Neurology, Istanbul, Turkey
[2]Acibadem University, School of Medicine, Department of Medical Sciences, Pediatric Health and Diseases, Istanbul, Turkey
[3]Istanbul University, Istanbul Medical Faculty, Department of Neurology, Istanbul, Turkey
[4]Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Neurology, Istanbul, Turkey

Highlights

- **Niemann-Pick disease type C (NPC) is a rare autosomal recessive disorder.**
- **Mutations in the NPC1 and NPC2 genes affect intracellular cholesterol metabolism.**
- **In the juvenile form of NPC, some patients have focal and/or generalized seizures.**
- **The seizures may be drug resistant in this rare disorder.**
- **A genetically diagnosed NPC with non-consanguineous parents is presented.**

Niemann-Pick disease type C (NPC) is a rare autosomal recessive disorder of intracellular cholesterol trafficking and synthesis caused by mutations in the NPC1 and NPC2 genes (1). Clinical presentation is highly heterogeneous, depending on the age of onset (2). In the juvenile form of NPC, one-third of individuals have focal and/or generalized seizures, and these seizures may be drug-resistant (3). Herein, we present a patient with genetically confirmed juvenile onset NPC with non-consanguineous parents in order to raise awareness about this rare and potentially treatable disease.

This 10.5-year-old male was healthy at birth and reached normal developmental milestones. His family history disclosed epilepsy in distant relatives and an attention deficit history. He presented with the first symptoms at the age of 6, with poor school performance, and received an initial diagnosis of attention deficit hyperactivity disorder. Two years later, abnormal behavior including anxiety and aggression were observed. At the age of 9, he experienced his first generalized tonic-clonic seizure with focal onset during sleep followed by Todd paresis. Staring spells with short duration, focal motor seizures, and myoclonia predominantly on the left arm and shoulder were also added to the clinical picture. Despite using multiple anti-seizure drugs including carbamazepine, valproate, clobazam, and sulthiame, focal motor seizures could not be controlled. Moreover, his clinical condition deteriorated progressively, and neurological examination showed moderate cognitive impairment measured by WISC-R (Intelligence Test for Children), ataxia, apraxia, dystonic posture on the left side and vertical supranuclear gaze palsy. Electroencephalography (EEG) revealed frequent focal spike-wave and multi-spike discharges on the frontocentral regions including parasagittal midline regions mainly on the right side and rarely generalized 2 Hz asymmetric spike and waves with preserved background activity. Cranial magnetic resonance (MR) imaging of 3 Tesla with thin sections was normal except for mild ventricular dilatation. Whole exome sequencing (WES) of the patient demonstrated two previously reported pathogenic variants in the NPC1 gene: (NPC1(NM_000271.5): c. 2861C >T (p. Ser954Leu)]. Segregation analysis showed compound heterozygous inheritance as the parents were carriers of each variant. After confirming the genetic diagnosis of NPC, oral miglustat treatment (400 mg/day) was started. The patient showed improvement in ataxia and abnormal behavior, and epileptic seizures were controlled.

Cite this article as: Altındağ E, Alanay Y, Baykan B, Dervent A. A Potentially Treatable Genetic Disorder Which Presented with Neuropsychiatric Involvement and Drug-Resistant Focal Epilepsy: Niemann-Pick Disease Type C. Arch Neuropsychiatry 2024;61:99–100.

Correspondence Address: Ebru Altındağ, İstanbul Florence Nightingale Hastanesi, Nöroloji Kliniği, İstanbul, Turkey • **E-mail:** altindagebru@gmail.com
Received: 29.01.2024, **Accepted:** 02.03.2024, **Available Online Date:** 25.05.2024

Drug-resistant focal epilepsy, along with slowly-progressive cognitive impairment and abnormal behavior in our patient indicated a need for detailed etiological investigation, after excluding other symptomatic etiologies such as cortical development disorders with MRI. Whole exome sequencing is recommended as a first-line test in these conditions and showed the presence of two different pathogenic variants, each inherited from one of the carriers in the NPC1 gene (4). Genetic diagnoses significantly provide precision treatment with miglustat as in our patient. An early diagnosis is mandatory since the treatment seems more efficient when started early in this rare disease (5). In conclusion, drug-resistant focal epilepsy with neuropsychiatric involvement prompted a genetic investigation leading to the diagnosis of NPC in our patient whose parents were non-consanguineous. The response to miglustat therapy has been remarkably favorable even at this late stage. Given the rarity of this condition, it is crucial to raise awareness of the disease to prompt consideration of the NPC diagnosis and facilitate genetic investigations.

Explanation: Our article was presented as an e-poster at the 59th National Neurology Congress.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- AE, DA; Design- AY; Supervision- AE, BB; Writing-AE ; Critical Reviews-BB.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Vanier MT. Niemann-Pick disease type C. Orphanet J Rare Dis. 2010;5:16. [Crossref]
2. Patterson MC, Mengel E, Wijburg FA, Muller A, Schwierin B, Drevon H, et al. Disease and patient characteristics in NP-C patients: findings from an international disease registry. Orphanet J Rare Dis. 2013;8:12. [Crossref]
3. Rangel DM, Melo MCA, Pedroso JL, Barsottini OGP, Sobreira-Neto MA, Braga-Neto P. Beyond the typical syndrome: understanding non-motor features in Niemann-Pick disease. Cerebellum. 2020;19:722–738. [Crossref]
4. Patterson MC, Clayton P, Gissen P, Anheim M, Bauer P, Bonnot O, et al. Recommendations for the detection and diagnosis of Niemann-Pick disease type C. An update. Neurol Clin Pract. 2017;7:499–511. [Crossref]
5. Berry-Kravis E. Niemann-Pick disease, Type C. Diagnosis, management and disease-targeted therapies in development. Semin Pediatr Neurol. 2021;37:100879. [Crossref]