Case Report

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Unawareness; The Reason of Delayed Diagnosis of Niemann Pick Disease Type C and the Birth of Another Involved Sibling

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ABSTRACT

Background: Niemann-Pick disease type C (NPC) is an autosomal recessive neurovisceral lysosomal storage disorder resulting from mutations in either the NPC1 or the NPC2 gene. It shows a broad spectrum of clinical phenotypes and a variable age at diagnosis. As most patients have normal routine examinations (MRI, cerebrospinal fluid, electrophysiology, and so on), its diagnosis is often a challenge, and the start of treatment delays for several years.

Case Report: We reported a 9-year-old boy who presented with Stuttered speech, hepatosplenomegaly, and up and downward gaze palsy whose Niemann Pick disease was not diagnosed during infancy due to unawareness. Dried blood spot assay and genetic study confirmed the diagnosis of Niemann Pick disease type C.

Conclusion: Due to the high rate of consanguineous marriages and NPC presentation with atypical phenotypes, more educational programs for pediatricians, hematologists, neurologists, endocrinologists, and clinicians help the appropriate and timely diagnosis and prevent another involved sibling.

Introduction

Niemann-Pick disease type C (NPC) is a rare progressive genetic disorder characterized by the body's incapability to transport cholesterol and other fatty substances like low-density lipoprotein inside cells.[1] Alterations in the trafficking of endocytosed cholesterol (NPC1 or NPC2 mutations) cause signs and symptoms[2] and lead to an abnormal increase of these substances within different tissues of the body, including brain tissue. Patients with NP-C usually develop a variety of progressive disabling neurological symptoms, including ataxia, vertical

supranuclear gaze palsy, gelastic cataplexy, spasticity, dystonia, severe liver disease, hepatosplenomegaly, interstitial lung disease, sleep disturbances, problems with speech and swallowing that worsen over time, impedance with feeding and progressive decrease of intellectual function.[3] Typically in patients with NPC, macrophages with abnormal cholesterol storage, so-called foam cells, can be identified in the bone marrow.[4] Cardiac involvement with cardiomegaly thickened left ventricular wall and substantial endocardial fibroelastosis have also been reported in NP-C patients.[5]

Age of onset and symptoms differs from one person to another, sometimes even among members of the same family. The clinical spectrum ranges from a fatal antenatal disorder to an adult-onset chronic neurodegenerative disease.[6]

The rarity of the disease and the scarcity of expertise result in misdiagnosis, delayed diagnosis, barriers to adequate care[6], and the birth of other siblings in the same family.

Mutations in the *SMPD1* gene and the enzyme acid sphingomyelinase deficiency are underlying defects in types A and B that do not occur in NPC. Niemann-Pick disease types A and B are now considered a different disorder called acid sphingomyelinase deficiency. National Organization for Rare Disorders (NORD) has a separate report on this disorder in the Rare Disease Database.[1]

The estimated disease incidence is 1 in 120,000 live births, but this likely represents an underestimate because the disease may be under-diagnosed due to its highly heterogeneous presentation.[7]

In IRAN, if a patient manifests suspicious signs and symptoms, screening of NPC is done with dried blood spot measured Lysosphingomyelin-509 (Lyso-SM-509). Measurement of combinations of biomarkers, such as Lyso-SM and Lyso-SM-509, allows distinction between NP-C and sphingomyelinase deficiencies (NP-A/B) as the increase of Lyso-SM in patients with NP-C is very small compared with that of patients with NP-A/B.[8]

Case Report

The patient was a nine-year-old Iranian boy. He was referred to our hospital with massive splenomegaly and hepatomegaly.

His symptoms had appeared from middle infancy. His mother referred her son to a physician for developmental delay and abdominal distention. After primary workup, bone marrow aspiration was performed by a pediatric physician. The hematologist reported large quantities of macrophages with abnormal cholesterol storage (foam cells) in the bone marrow. Simultaneously, the patient had a dried blood spot screen about Niemann's pick and Gaucher's diseases. All enzymatic results were reported without any specific diagnosis, and the patient was discharged from the hospital.

At two years old, intellectual disability and speech delay added to previous symptoms stimulating the mother's anxiety. She sought medical help again to find a solution. The patient was undergoing bone marrow aspiration and enzyme assay for Niemann pick and Gaucher diseases by DBS for the second time. All results were normal. Follow-up procedure was the only advice of the physician to parents.

Due to the boy's learning disabilities at school, his parents decided to refer their child to our hospital.

Past medical history revealed that there is at least one neglected point. All medical process was revised. Stuttered speech and hepatosplenomegaly were evident. Moreover, up and downward gaze palsy was detected.

It seems our colleagues, residing at the birth city of the patient, have noticed lysosomal storage disorders well, but probably they did not have had sufficient awareness on two subjects; firstly, they did not know the main signs and symptoms of the different types of lysosomal storage disorders. Also, they did not have information regarding the different nature of NPC. Therefore, despite the elevation of lipid in bone marrow, the negative screening for Niemann pick type A, B, and Gaucher disease

ruled out the diagnosis of LSD (S).

In the first time after admission, we supplied dried blood spots for assay of Lyso-SM and Lyso-SM-509 by ACTELION company, the only official reference that organized NPC diagnosis in Iran. Because of the possibility NPCof, a genetic study was done at the same time without wasting time. All results suggested npc, and promptly, treatment was started.

Unfortunately, his six-month sibling with NPC was admitted alongside. Lack of inclusive acknowledgment on NPC and other LSD(S) caused a child to be involved with a sibling and double the family's problems.

Discussion

NPC is a rare genetic neurovisceral disorder, with an estimated minimal incidence of 1/120000 live births. This value should be considered a minimal estimate since atypical phenotypes may not be suspected clinically or missed by the diagnostic laboratory.[2] It is generally supposed that NPC disease is underdiagnosed (notably in its less severe clinical forms in adults). Many patients suspected of NPC are not referred to specialized clinical centers for a definite diagnosis.

In addition, a high rate of consanguineous marriages in IRAN can increase NPC occurrences that show autosomal recessive inheritance and is pan-ethnic.[2,9]

Conclusion

Therefore, the high rate of consanguineous marriages and NPC presentation with atypical phenotypes and clinicians lack of awareness of the most common and infrequent symptoms and diagnosis procedure show the need to more educational program for pediatricians, hematologists, etc., neurologists and endocrinologists.

It is enough to know that if only local physicians were educated on the diagnosis; another involved sibling would have been prevented.

Conflict of Interests

Authors have no conflict of interests.

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