

## Niemann-Pick Diseases: The Largest Iranian Cohort with Genetic Analysis

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### Abstract

**Objectives:** Niemann-Pick diseases (NPD) is an autosomal recessive inherited lysosomal lipid storage disorder which occurs due to a defect in cellular cholesterol trafficking, leading to excess lipid accumulation in multiple organ systems such as the brain, lungs, spleen, and liver. SPMD1-associated disease includes classic infantile and visceral NPD type A and B respectively. Type C NPD is subacute or juvenile.

### Materials & Methods

During 2012-2016, the patients who had the clinical and biochemical signs and symptoms of different types of NPD, underwent genetic analysis. All patients were collected from five provinces in Iran (Razavi Khorasan, South Khorasan, Khozaestan, Isfahan and Tehran province). Sanger sequencing of the candidate genes for NPD was performed followed by bioinformatics analysis to confirm the types of NPD and to identify novel mutations. All patients underwent full clinical assessment.

**Results:** We present two cases with NPD type A, six cases with NPD type B, and 11 cases with type C with various enzymatic defects identified in these cases. Within these 19 patients, we present 9 previously reported mutations and 10 novel mutations causing NPD.

**Conclusion:** This study is the largest Iranian study for NPD analysis ever. Our report demonstrates that NPD has a variable age of onset and can present early in life. We investigated the clinical and genetic manifestations of a large Iranian cohort. Understanding the variable

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presentation of NPD will allow for clinicians to have a high index of suspicion for the disease.

**Keywords:** Niemann-pick disease (NPD); Genetic analysis; Autosomal recessive; Iran

## Introduction

Niemann-Pick Diseases (NPD) is a disorder that affects multiple organ systems. It has an extensive range of presenting symptoms which differ in severity. NPD is classified into four types: A, B, C1, and C2. These types are classified based on the genetic cause, clinical signs and presenting symptoms (1). NPD type A and B are also known as a SMPD1-associated disease which constitutes different clinical phenotypes of a primary sphingomyelin storage disorder resulting from acid sphingomyelinase deficiency due to SMPD1 gene mutations (2-4). The classical phenotype of NPD is often described as hepatosplenomegaly, with progressive ataxia, dystonia, and dementia. NPD type A is the most common type present in infants and is characterized by jaundice, hepatomegaly, failure to thrive, progressive deterioration of the nervous system and profound brain damage most often leading to death before 18 months of age (5). Type A is most common amongst those from Ashkenazi (eastern and central European) Jewish descent (6).

In NPD type B patients, hepatosplenomegaly is often present which may be severe in the presence or absence of signs of liver failure. Serum low-density lipoprotein (LDL)-cholesterols and triglycerides are often elevated in NPD, although high-density lipoprotein (HDL)-cholesterol is found to be at low levels. Another clinical sign present in some type B cases is a distinct cherry-red spot in the macula (7). Type B patients have no overt signs of central nervous system involvement but frequently have compromised pulmonary function (6). NPD type C can present in infancy, childhood, or adulthood. Neonates may present with severe ascites due to severe liver disease or respiratory failure as

well as renal failure (8, 9). Newborns presenting without liver or pulmonary disease, often present with hypotonia and developmental delay (1).

NPD type C most commonly develops in late childhood with most patients not surviving to the second decade of life (2-4). Other phenotypes include fatal neonatal liver disease, delayed motor development and early infantile onset with hypotonia. Adult variations in the phenotype include onset of psychosis and dementia, juvenile dystonic lipidoses, DAF (downgaze paresis, ataxia, foam cells) syndrome, adult dystonic lipidoses, dystonia, and organomegaly, all of now recognized as presentations of NPD (9-11).

In this case series, we describe 19 cases to illustrate the clinical manifestations of NPD and further discuss the variations in the genetics findings and biochemistry.

### **Case Presentation**

In this study, we present 19 patients with ranging types of NPD including Type A, B, C, and C1. All cases who presented, were admitted to their local hospital due to onset of health complications. Each patient underwent a complete clinical

assessment (Table 1). Each case also underwent the appropriate biochemical investigations, which revealed enzymatic defects. Post-genetic counseling and molecular investigations such as Sanger sequencing were performed to confirm the clinical diagnosis of NPD and determine the type of NPD present in all patients.

Written informed consent was obtained from all subjects and the study protocol has been approved by the Regional Ethics Committee in the field of human research, in their local universities.

Two cases had NPD type A, both of whom died in infancy. Six patients had type B NPD of which four died by 4.5 years of age and two are currently alive and under three years of age. Eleven patients had/ have NPD type C/ C1. Five of the patients were born to parents not-related and 14 to consanguineous parents (Table 1). Fourteen patients had hepatosplenomegaly and elevated liver enzymes, and 15 patients had developmental and psychomotor regression. Two cases had an auditory impairment and four with a visual impairment. In 10 cases we identified novel mutations predicted likely pathogenic.

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**Table 1:** Each patients' clinical findings including and genetic information with mutation identified

Case Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
NPD Type	A	A	B	B	B	B	B	B	C	C1	C1	C1	C1	C1	C1	C1	C1	C1	C1
Current Age	Dead at 6 months old	Dead at 2.5 years old	Dead at 3 years old	Dead at 4.5 years old	Dead at 3 years old	Dead at 1.5 years old	Alive 1.5 years old	Alive 2.4 years old	Dead at 2 years old	Alive 3.5 months	Alive 6 months	Alive 4.9 years	Dead at first	Dead at 2.4 years old	Alive 28.5 years old	Alive 29.6 years old	Alive 46 years old	7 months	Alive 24 years old
Gender	Male	Male	Female	Male	Female	Male	Male	Female	Female	Male	Female	Male	Female	Female	Male	Female	Male	Female	Female
Ethnicity	Ashkhan	Ashkhan	Ashkhan	Baluch	Lor (Baluch)	Ashkhan	Fars	Fars	Baluch	Fars	Fars	Fars	Fars	Fars	Fars	Fars	Fars	Fars	Turk (Azeri)

  

Compatibility of parents' Other family members NPD, if any, type	Medical & Family History																			
	Second cousin	First cousin	First cousin	First cousin	First cousin	First cousin	First cousin	First cousin	First cousin	First cousin	First cousin	First cousin	First cousin	First cousin	First cousin	First cousin	First cousin	First cousin	First cousin	First cousin
Age of Diagnosis	6 months	5 months	6 months	6 months	6 months	7 months	Unknown	Unknown	6 months	3 months	5 months	4.5 years	At birth	6 months	27 years	28 years	44 years	6 months	25 years	
Second cousin (Y/N)	N	N	N	N	N	Y	Y	Y	N	Y	Y	Y	N	N	N	N	N	N	N	N
First cousin (Y/N)	N	N	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Half-cousin (Y/N)	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Siblings (Y/N)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Hypertrophy (V/N)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Any intellectual disability (V/N)	Y	Y	N	Y	N	N	Y	Y	N	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y
Developmental regression (V/N)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y
Gait paresis (V/N)	N	N	N	N	N	N	N	N	N	N	N	N	NA	Y	Y	Y	Y	Y	Y	Y
Epilepsy (V/N)	N	Y	N	N	N	N	N	N	N	N	N	N	NA	N	N	N	N	N	N	N
Mental illness (V/N)	Y	Y	Y	N	N	N	N	N	N	N	N	N	NA	Y	Y	Y	Y	Y	Y	Y
Cardiac abnormalities (V/N)	N	N	N	N	N	N	N	N	N	N	N	N	NA	N	N	N	N	N	N	N
Other impairment (V/N)	N	N	N	N	N	N	N	N	N	N	N	N	NA	Y	Y	Y	Y	Y	Y	Y
Visual impairment, if any, severity	N	Cherry-red spot	N	N	N	N	Cherry-red spot	N	Cherry-red spot	N	N	N	NA	Y	N	N	N	N	N	N



## Discussion

In this case series, we have presented 19 different patients from different families and nationality with NPD type A, B, C, and C1. Data were consolidated for the clinical manifestations and biochemical findings as well as genetic investigations performed. This case series provides clinical data on 19 patients with NPD with 10 novel previously undescribed mutations along with formerly reported mutations. Clinical symptomatology and disease progression in NPD are markedly affected by the age of disease onset of neurological manifestations also suggested elsewhere (11).

Overall, the main complication present in most cases was liver disease, affecting 14 patients out of 19. Liver disease is known to be a cause of significant morbidity and mortality in NPD. The diagnosis of NPD type C should be considered in patients with unexplained neonatal hepatitis especially in the presence of splenomegaly (12). NPD should also be high on the differential diagnosis in the presence of systemic symptoms such as neonatal jaundice and isolated splenomegaly, neurological symptoms such as dystonia, dementia, cataplexy and supra nuclear gaze palsy which may occur in patients (13). In this case series, we have presented 10 patients who were female and 9 males. All cases with type A or B NPD had mutations in *SMPDI* and all those with NPD type C on *NPC1*. Identification of mutations in *NPC1* is challenging due to the relatively large nature of the gene and majority of the mutations being private (12).

There are 3 types of NPD that the primary biological defect is different (13). NPD types A and B are autosomal recessive lysosomal storage diseases caused by the deficient activity of acid sphingomyelinase due to mutations in the *SMPDI*.

Genetic variants which are considered as disease causing are distributed in *SMPDI* gene. Most of these variants are missense or frameshift mutations (14). In this case series, eight of the cases had mutations in *SMPDI* predicted to be pathogenic or likely pathogenic. Studies have shown that the *SMPDI* is preferentially expressed from the maternal chromosome (15). In Iran, the first molecular diagnosis of NPD type A was reported. It had detected a novel deletion in *SMPDI* gene (16). A novel mutation in exon 9 of *NPC1* gene was reported from Khorasan Province, Iran (17).

Consanguineous marriage is common upon our region (18) and consanguinity was observed between the parents of 14 cases; however, both developmental and psychomotor regression were observed in all but two cases presented. Mongolian spots and cherry-red spot were present in three cases. Case 13 and 14 were deceased prior to the final genetic investigations were performed.

**In conclusion**, these findings in NPD have clinical implications for genetic counseling. Our study provides a large number of patients with varying presentations and novel mutations. In suspected NPD, clinicians should confirm the carrier status of both parents and evaluate other first-degree relatives to provide families with accurate genetic counseling.

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**Author's contribution:** Somayyeh Hashemian and Ehsan Gayoor designed the study. Ehsan Ghayoor, Somayyeh Hashemian and Najmeh Ahangari collected all the cases and analyzed the data and collected the data. Other authors collected the clinical findings and genetic assay. Gholamreza Shariati supervised the study.

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

#### Conflict of interest

The authors declare that they have no conflicting interests.

#### References

1. Patterson M. Niemann-Pick Disease Type C. 2000 Jan 26 [Updated 2013 Jul 18]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1296/>
2. Lynn R, Terry RD. Lipid histochemistry and electron microscopy in adult niemann-pick disease. *Am J Med* 1964;37:987-94.
3. Schneider EL, Pentchev PG, Hibbert SR, Sawitsky A, Brady RO. A new form of Niemann-Pick disease characterised by temperature-labile sphingomyelinase. *J Med Genet* 1978;15:370-4.
4. Yan X, Lukas J, Witt M, Wree A, Hubner R, Frech M, et al. Decreased expression of myelin gene regulatory factor in Niemann-Pick type C 1 mouse. *Metab Brain Dis* 2011;26:299-306.
5. Simonaro CM, Desnick RJ, McGovern MM, Wasserstein MP, Schuchman EH. The demographics and distribution of type B Niemann-Pick disease: novel mutations lead to new genotype/phenotype correlations. *Am J Hum Gen* 2002;71:1413-9.
6. Schuchman EH, Desnick RJ. Types A and B Niemann-Pick disease. *Mol Gen Metab* 2017;120:27-33.
7. Schuchman EH. The pathogenesis and treatment of acid sphingomyelinase-deficient Niemann-Pick disease. *J Inherit Metab Dis* 2007;30:654-63.
8. Zheng Z, Cheng C, Zhao W, Feng Q, Li C, Lou T. Case Report Renal failure and ascites in a patient with Niemann-Pick disease: case report and literature review. *Int J Clin Exp Me* 2016;9:4800-4.
9. Marie T Vanier. Niemann-Pick disease type C. *Orphanet J Rare Dis* 2010;5:16.
10. Uc EY, Wenger DA, Jankovic J. Niemann-Pick disease type C: two cases and an update. *Mov Disord* 2000;15:1199-203.
11. Jahnova H, Dvorakova L, Vlaskova H, Hulkova H, Poupetova H, Hrebicek M, et al. Observational, retrospective study of a large cohort of patients with Niemann-Pick disease type C in the Czech Republic: a surprisingly stable diagnostic rate spanning almost 40 years. *Orphanet J Rare Dis* 2014;9:140.
12. Kelly DA, Portmann B, Mowat AP, Sherlock S, Lake BD. Niemann-Pick disease type C: diagnosis and outcome in children, with particular reference to liver disease. *J Pediatr* 1993;123:242-7.
13. Karimzadeh P. Juvenile type of Niemann-Pick type C disease and our study in Iranian NPC patients. *Iran J Child Neurol* 2015;9(4):5-6.
14. Schiffmann RJJ. Niemann-Pick disease type C: from bench to bedside. *JAMA* 1996;276:561-4.
15. Fotoulaki M, Schuchman EH, Simonaro CM, Augoustides-Savvopoulou P, Michelakakis H,

- Panagopoulou P, et al. Acid sphingomyelinase-deficient Niemann-Pick disease: novel findings in a Greek child. *J Inherit Metab Dis* 2007;30:986.
16. Galehdari H, Tangestani R, Ghasemian S. New single nucleotide deletion in the SMPD1 gene causes niemann pick disease type A in a child from Southwest Iran: a case report. *Iran J Pediatr* 2013;23:233-36.
17. Noroozi Asl S, Vakili R, Ghaemi N, Eshraghi P. The Report of Three Rare Cases of the Niemann-pick Disease in Birjand, South Khorasan, Eastern Iran. *Iran J Child Neurol* 2017;11(3):53-6.
18. Moghaddam HM, Esfehni RJ, Panah NY, Esfehni AJ. Consanguinity and isolated atrial septal defect in North East of Iran. *Ann Saudi Med* 2014;34(2):147-52.