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THE EARLY DIAGNOSTIC OF NIEMANN-PICK DISEASE TYPE A CAUSED BY *c.996del* AND *c.1252C>T* IN *SMPD1* GENE: A CASE STUDY

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INTRODUCTION & AIM

Niemann-Pick disease Type A (MIM 257200, NPD type A) is a rare congenital autosomal recessive hereditary condition. It is caused by the presence of causal nucleotide variants in the gene *SMPD1* (NM_000543.5), resulting in deficiency of the enzyme Acid Sphingomyelinase (ASM), encoded by *SMPD1*. This, in turn, leads to an abnormal lysosomal accumulation of sphingomyelin, causing tissue and organ damage. If untreated, it can result in severe complications and death. Therefore, early diagnosis of NPD type A is crucial. The multi-methodological clinical diagnostic of NPD type A includes measurements of enzyme activity of ASM, genetic analysis aimed to detect causal nucleotide variants in *SMPD1*, and a genetic and genealogical study of proband's family.

METHOD

The activity of ASM was measured in Dried Blood Spots (DBS) by High-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). DNA was isolated from DBS and Sanger sequencing of *SMPD1* was performed via the BigDye® Terminator v3.1 Cycle Sequencing Kit (Thermo Fisher Scientific, USA, Waltham) in accordance with the manufacturer's protocols. Amplification was performed on Bio-Rad T100 (Bio-Rad, USA, Santa Rosa) and ProFlex (Thermo Fisher Scientific, USA, Waltham) thermocyclers. Capillary electrophoresis was performed on ABI 3500XL automated DNA sequencer (Thermo Fisher Scientific, USA, Waltham). The obtained sequences were compared with RefSeqGene reference sequences from the NCBI database. The schematic of workflow is shown in (Figure 1).

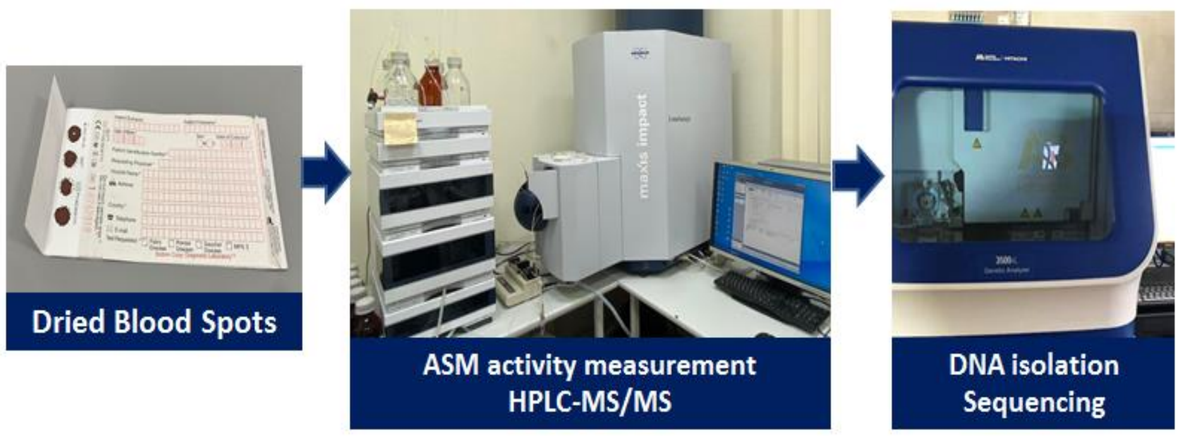

Figure 1. Schematic of workflow

RESULTS & DISCUSSION

The Patient III-3 was referred to our center based on the overall clinical picture. The HPLC-MS/MS detected significant decrease of ASM activity in patient's DBS, 0.07 umol/L/h (cut-off > 1.05 umol/L/h) (Figure 2).

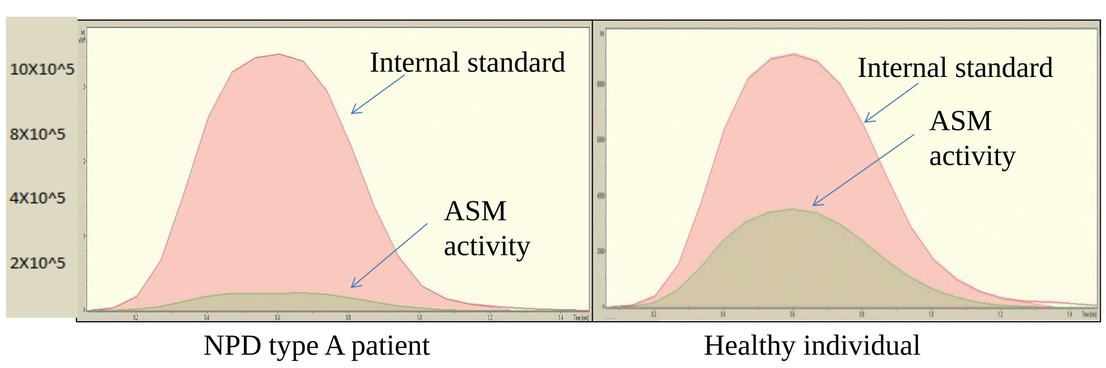

Figure 2. Enzyme activity of ASM measured by HPLC-MS/MS in patient III-3 vs Healthy individual

Sanger sequencing of *SMPD1* gene revealed PSVs c.996del, (p.Phe333Serfs*52) and c.1252C>T, (p.Arg418*) in heterozygous state (Figure 3). Subsequent genetic and genealogic studies of the proband's family were performed (Figure 4).

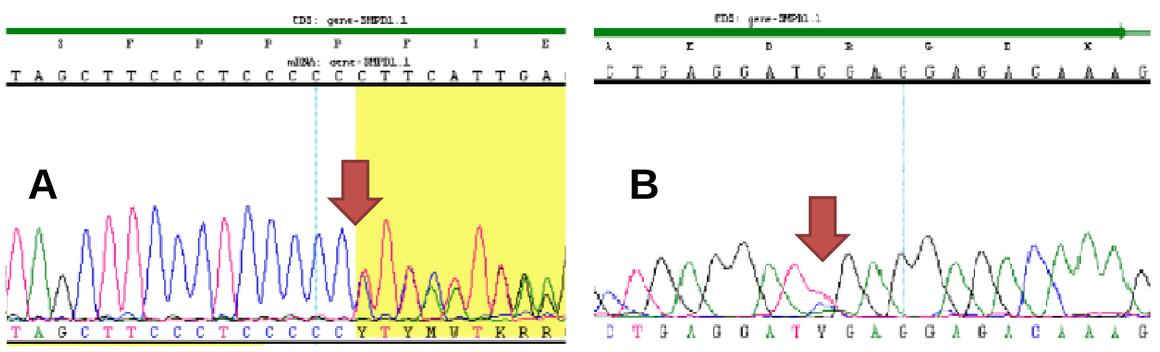

Figure 3. Partial genomic sequence of *SMPD1* gene of Patient III-3 compound heterozygous for the variants c.996del (A) and c.1252C>T (indicated by red) (B).

Further segregation analysis showed each variant inherited from one of the genetically unrelated healthy parents. The family received genetic counseling regarding the findings. Another two siblings were not carriers of these variants in *SMPD1* and their ASM activity was in the normal range. However, the same nucleotide variants were found in the third sibling, Patient III-5, whose ASM activity levels were below the normal range (0.16 umol/L/h) (Figure 4).

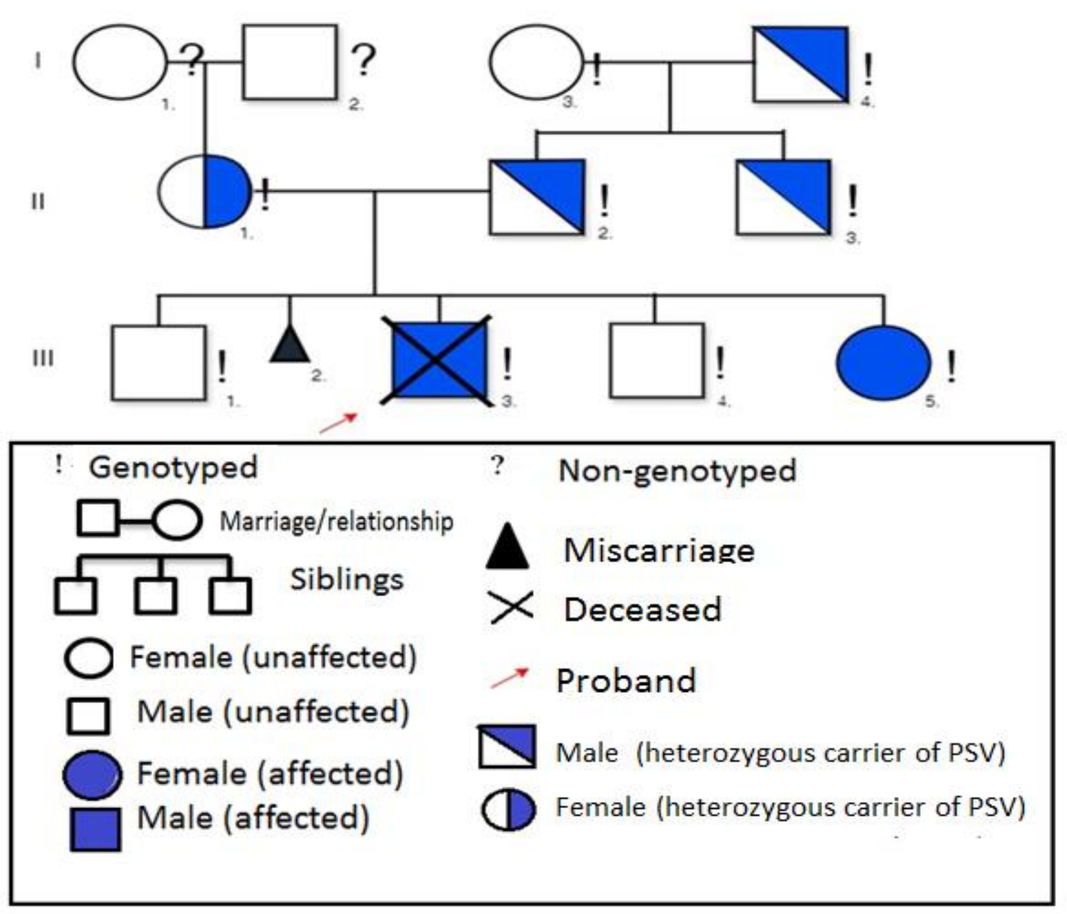

Figure 4. Genealogical analysis of the proband family

CONCLUSION

Without the diagnostic approach including clinical, biochemical, genetic and genealogical analysis this patient would have missed a timely diagnosis of NPD type A. This highlights an importance of multi-methodological approach to diagnostic of rare genetic diseases.

INFORMED CONSENT STATEMENT

All study participants, or their legal guardians, provided signed informed consent prior to study enrollment in accordance with declaration of Helsinki.