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Commentary

An overview of clinical, molecular, and therapeutic approaches to Niemann-Pick disease

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In animal cells (especially humans), there is an enzyme called acid sphingomyelinase (ASM) (EC 3.1.4.12) which can break the large molecule of sphingomyelin and convert it into smaller structures of ceramide and phosphorylcholine [1]. ASM has three isoforms: isoform I (lysosomal or extracellular) which has catalytic activity and plays a role in breaking down lipid substrates and transporting cholesterol from the lysosomal membrane, and isoforms II and III which have no catalytic activity and are unable to bind to the Zn^{2+} cofactor [2,3]. Any mutation in the gene producing this enzyme leads to Niemann-Pick disease (NPD). Following the mutation, the substrate accumulates in the lysosome of different organs, leading to the development of clinical symptoms of the disease [4]. Since the inheritance pattern of NPD is autosomal recessive, this disease has four clinical variants in terms of phenotype: A, B, C, and E, of which the first three types are the most common. The average incidence of NPD (depending on the type) is 1 in 150,000 people and is most common in Ashkenazi Jews [5]. The diagnosis of the disease depends entirely on the type of the disease and the severity of the disease symptoms, but the measurement of ASM levels in the blood of patients and the Philippine test are routinely used [6]. In addition to supportive care, approaches such as enzyme replacement therapy (ERT) [7], substrate replacement therapy (SRT) [8], bone marrow transplantation (BMT) [9], chaperone therapy [10], and gene therapy [11,12] are used to alleviate the symptoms of the disease. Recently, most studies have focused on the last approach.

Clinical variant A (early-onset form) often affects infants neuroviscerally. In this form of the disease, which is the most severe form of NPD (due to missense and frameshift mutations in the *SMPD1* gene), there is no sphingomyelinase enzyme in the cell to break down the lipid substrate [13]. Type A often affects children between three months and three years old, and the most common complication of NPA is hepatosplenomegaly, which worsens if left untreated. The most common signs and symptoms of this type of disease include very poor growth of the child, various respiratory infections, lung involvement, visual impairment, and muscle weakness [14,16]. NPA has a poor prognosis and is usually fatal by the age of three. Recent research has shown that there is a direct relationship between clinical symptoms (phenotype) and the genetics of patients (genotype). Thus, one or several different mutations in the *SMPD1* gene causes various clinical symptoms. In addition to the latest report by Hosseini *et al.* [17], some researchers have recently reported cases of NPD type A. For example, studying a 7-month-old Thai girl, Ngoenmak *et al.* found that she had symptoms similar to NPD type A. In the child, they observed symptoms such as hepatosplenomegaly, neurodevelopmental delay, rough face, cherry red spots, hypotonia, lack of growth, and Mongolian spots. Also, according to the Sanger sequencing results, they found that this patient had a homozygous pathogenic new variant (c.1214T>C (p. Leu 405Pro)) in the *SMPD1* gene. Finally, due to a lack of timely diagnosis and treatment, the child died at the age of 4 due to respiratory failure and severe

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Competing of Interests

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