A Rare case of Sanfilippo syndrome type "C"

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ABSTRACT

Sanfilippo syndrome or mucopolysaccharidosis type III is a rare autosomal recessive neurodegenerative lysosomal storage disease. The prevalence of Sanfilippo syndrome is 1 in 100,000 live births. Here, we are presenting a case of an 8-year-old female child who presented with mild intellectual disability, sleep deprivation, and hyperactivity. The patient was diagnosed with Sanfilippo syndrome type C. The diagnosis was made by increased heparan sulfate in urine analysis and exome sequencing showed homozygous missense variant c.1622>T (p.Ser541Leu) in exon 17 of HGSNAT gene that leads to amino acid substitution from serine to leucine at codon 541. We are presenting this case because several diseases have similar clinical presentation and there is difficulty in making definitive diagnosis. The importance of early diagnosis is to prevent complications and recurrence of the disease in subsequent pregnancies.

Key words: *Hyperactivity, Intellectual disability, Mucopolysaccharidosis, Sanfilippo syndrome, Sleep deprivation*

Lysosomal storage disorders (LSDs) are a group of more than 50 inherited monogenic disorders. Each is caused by a deficiency of an enzyme responsible for the degradation of a metabolic product, whose accumulation results in lysosomal malfunction and disease. The classification of LSDs primarily depends on storage material and secondarily by the enzyme whose activity has been impeded. Sanfilippo syndrome or mucopolysaccharidosis type III (MPS III) is a rare autosomal recessive neurodegenerative LSD. The prevalence of Sanfilippo syndrome is 1 in 100,000 live births.

There are four subtypes of MPS III, type A (mutation in SGSH gene and leads to deficiency of heparan sulfamidase enzyme) [1], type B (mutation in NAGLU gene and leads to deficiency of N-acetylglucosaminidase enzyme) [2], type C (mutation in HGSNAT gene and leads to deficiency of heparan-alpha-glucosaminide N-acetyltransferase enzyme) [3], and type D (mutation in GNS gene and leads to deficiency of N-acetylglucosamine-6-sulfatase enzyme) [4]. Due to enzyme deficiency, heparin sulfate or glycosaminoglycans (GAGs) accumulate in lysosomes and lead to defective cellular metabolism.

Among all subtypes, lifetime risk at birth of type A is most common, followed by type B, and type C is very rare. The incidence of MPS III C is between 0.00 and 0.42/100,000 live births [5-9]. The relative frequency of MPS IIIC is 1.2% among all patients' diagnosed with LSDs in India [10]. The clinical progression of MPS IIIC is variable, as disease initially presents with developmental delay after a period of normal development followed by severe behavioral problems and later by hyperactivity. Some children with MPS IIIC present with coarse facial features, language developmental delay, hepatomegaly, and epilepsy. With the progressive cognitive decline, patients eventually regress to fully bedridden and vegetative state that results in significantly diminished life expectancy. The mean age of death in MPS IIIC is 23.43±9.47 years, due to fatal respiratory infections (i.e., pneumonia) [11]. Here, we are presenting a case of an 8-year-old female child who was diagnosed with Sanfilippo syndrome type C.

CASE REPORT

An 8-year-old female patient presented to the pediatrics department with the chief complaint of mild intellectual disability, developmental delay, sleep deprivation, and hyperactivity. Since the age of 4 years, the patient presented with developmental delay with previously normal development and later led to sleep deprivation and hyperactivity at the age of 6 years. The patient's parents consulted several primary care physicians, neurologists, psychiatrists, and pediatricians since appearance and progression of symptoms and she was advised for several investigations (computed tomography, magnetic resonance imaging [MRI] brain, ultrasonography abdomen, electroencephalogram [EEG], complete blood count, thyroid, renal, and liver function tests, brain stem evoked response audiometry, Binet–Kamat intelligence test, Vitamin B_{12} level, erythrocyte sedimentation rate, and urine examination) to reach definitive diagnosis, but all investigations were within normal limit. Hence, the definitive diagnosis was not

made and the patient was started on symptomatic treatment but did not show any signs of improvement.

When the patient presented to us at the age of 8 years, on taking detailed history, the patient's parents told that the patient had mild intellectual disability and abnormal behavior, as she used to be very aggressive sometimes such as throwing the objects, temper tantrums, avoid to go to school, and cries a lot when see school van in the morning, screaming for no apparent reason, and fearless. The patient used to remain awake during late nights and played by herself in the middle of the night (sleep deprivation). They also complained of hyperactive behavior, as she could not sit still at one place, she used to visit neighbor or playground anytime during the day or in midnight, difficult to dress, etc. The patient's parents told that these symptoms presented by her were progressive since the age of 4 years. There was no history of previous hospitalization. Antenatal and perinatal history, family, and allergy history were not significant.

On examination, the patient appeared alert, without any facial dysmorphism, cyanosis, icterus, clubbing, hepatomegaly, and lymphadenopathy. Anthropometry including height 117.4 cm, weight 24 kg, and body mass index 17.51 kg/m^2. After detailed history, several differentials of the signs and symptoms presented by the patient were analyzed that were mucopolysaccharidosis, autism spectrum disorder with hyperactivity, Rett's syndrome, Heller's syndrome, attention-deficit hyperactivity disorder, and Landau–Kleffner syndrome.

Urine heparan sulfate, quantification showed higher values of 71.3 mg/mM (normal range 5.7–12.9 mg/mM). Clinical exome sequencing was performed to diagnose any genetic or metabolic disorder which showed homozygous missense variant c.1622 >T (p.Ser541Leu) in exon 17 of HGSNAT gene that led to amino acid substitution from serine to leucine at codon 541. The allele frequency of this gene variation was 0.0132%.

Normal EEG and MRI brain results ruled out the Landau–Kleffner syndrome. Increased urine heparan sulfate and clinical exome sequencing ruled out other differentials and MPS IIIC was diagnosed. As, no definitive treatment of the disease is present still so, symptomatic treatment with cognitive behavioral therapy, speech therapy, and occupational therapy was started and the patient was called for regular follow-up every month. The patient's parents reported improvement in hyperactivity and school performance after starting symptomatic treatment with occupational therapy.

DISCUSSION

MPS III is a rare autosomal recessive neurodegenerative LSD that primarily affects the brain and spinal cord. In this disease, there is a deficiency of different enzymes which leads to defective metabolism of heparin sulfate in lysosomes, leading to accumulation of heparin sulfate in lysosomes and impaired cellular metabolism. GAGs are chains of sugar molecules, which are found in the extracellular matrix and cell membrane and stored in the secretory granules.

Signs and symptoms of MPS IIIC begin to appear between 2 and 6 years of age [12]. The affected infants appear normal initially. MPS IIIC is progressive and separated into clinical stages. In the first stage, the child presents with delayed speech and mild coarse facial abnormalities. The affected children are prone to sinus and ear infections, diarrhea, enlarged tonsils, and hepatosplenomegaly. The children are hyperactive and aggressive, with frequent temper tantrums and fearlessness. The minor bone deformities are also common. In the second stage, there are sleep deprivation, walking and pacing, crying, and screaming for no apparent or clinically diagnosed reason. They are compelled to chew on things, throw objects, and their behavior becomes very difficult. Overtime, speech and cognitive skills decline. In the last stage, the child will lose the ability to walk, talk, and eat on his own and become dependent on caregivers. The slightest infection in this stage can result in death.

Héron *et al.* reported clinical characteristics of 17 patients presented with MPS IIIC as language delay (92%), coarse features (85%), abnormal behavior (77%), hepatomegaly (39%), autism spectrum disorder (8%), and epilepsy (8%) [6]. Ruijter *et al*. reported that the first clinical signs and symptoms for patients with MPS IIIC appeared at a mean age of 3.5 years. They included delayed speech development (92%), delayed motor development (83%), behavioral problems (83%), deterioration of speech (75%), sleeping problems (50%), diarrhea (58%), and deterioration of walking (17%) [11]. Van de Kamp *et al*. reported that the first signs appeared before the age of 4 years in 23% of 23 patients diagnosed with MPS IIIC, and dementia appeared before the age of 6 years in 33% of patients [13].

The diagnosis of MPS IIIC can be made by urine analysis which shows elevated levels of heparan sulfate in the early morning urine sample as reported by Hurst *et al*. [14], gene sequencing, and enzyme assay of skin fibroblasts and white blood cells [15-18]. As in the case reported here, increased heparan sulfate was observed. The mean age of diagnosis is between 4.5 and 19 years. The prenatal diagnosis of Sanfilippo syndrome can be made by chorionic villus sampling and amniocentesis [19]. The newer diagnostic technique is whole genome or exome sequencing, which allows screening of the entire genome or protein-coding region. It provides a standard method to test any subject for all sequencing abnormalities as reported by Fedele [20]. It was utilized in the present case which showed homozygous missense variant in exon 17 of HGSNAT gene and was helpful in the final diagnosis of the syndrome.

The treatment of MPS IIIC is only supportive, as there is the absence of curative treatment. Several therapies are under research such as enzyme replacement therapy, bone marrow replacement therapy, gene therapy, and the use of genistein (an isoflavone purified form of soy that exhibits ability to reduce heparin sulfate level) as reported by Piotrowska *et al*. [21]. The present case also reported improvement with supportive and occupational therapy. The expected life expectancy of MPS IIIC is late teens or early twenties (23.43±9.47 years) [22,23]. The common reason of death of the patient is due to respiratory infections, mostly pneumonia.

CONCLUSION

The importance of early diagnosis is to prevent systemic life-threatening complications and recurrence of the disease in subsequent pregnancies.

REFERENCES

1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The Metabolic and Molecular Bases of Inherited Disease. New York: McGraw-Hill; 2001. p. 3421-52.
2. Kresse H. Mucopolysaccharidosis 3 A (Sanfilippo A disease): Deficiency of a heparin sulfamidase in skin fibroblasts and leucocytes. Biochem Biophys Res Commun 1973;54:1111-8.
3. Von Figura K. Human alpha-N-acetylglucosaminidase. 1. Purification and properties. Eur J Biochem 1977;80:523-33.
4. Klein U, Kresse H, Von Figura K. Sanfilippo syndrome Type C: Deficiency of acetyl-CoA: Alpha-glucosaminide N-acetyltransferase in skin fibroblasts. Proc Natl Acad Sci U S A 1978;75:5185-9.
5. Baehner F, Schmiedeskamp C, Krummenauer F, Miebach E, Bajbouj M, Whybra C, *et al*. Cumulative incidence rates of the mucopolysaccharidoses in Germany. J Inherit Metab Dis 2005;28:1011-7.
6. Héron B, Mikaeloff Y, Froissart R, Caridade G, Maire I, Caillaud C, *et al*. Incidence and natural history of mucopolysaccharidosis Type III in France and comparison with United Kingdom and Greece. Am J Med Genet A 2011;155A:58-68.
7. Hult M, Darin N, Von Döbeln U, Månsson JE. Epidemiology of lysosomal storage diseases in Sweden. Acta Paediatr 2014;103:1258-63.
8. Al-Jasmi FA, Tawfig N, Berniah A, Ali BR, Hertecant JL, Bastaki F, *et al*. Prevalence and novel mutations of lysosomal storage disorders in United Arab Emirates: LSD in UAE. JIMD Rep 2013;10:1-9.
9. Krabbi K, Joost K, Zordania R, Talvik I, Rein R, Huijmans JG, *et al*. The live-birth prevalence of mucopolysaccharidoses in Estonia. Genet Test Mol Biomarkers 2012;16:846-9.
10. Kadali S, Kolusu A, Gummadi MR, Undamatla J. The relative frequency of lysosomal storage disorders: A medical genetics referral laboratory's experience from India. J Child Neurol 2014;29:1377-82.
11. Ruijter GJ, Valstar MJ, Van de Kamp JM, Van der Helm RM, Durand S, Van Diggelen OP, *et al*. Clinical and genetic spectrum of Sanfilippo Type C (MPS IIIC) disease in the Netherlands. Mol Genet Metab 2008;932:104-11.
12. "A Guide to Understanding MPS III". Available from: http://www.web.archive.org. [Last accessed on 2011 Jul 08; Last accessed on 2019 Mar 13].
13. Van de Kamp JJ, Niermeijer MF, Von Figura K, Giesberts MA. Genetic heterogeneity and clinical variability in the Sanfilippo syndrome (TypesA, B, and C). Clin Genet 1981;20:152-60.
14. Anna CE, David Z, Brenda C. "Mucopolysaccharidosis Type III". United States National Library of Medicine; 2017. Available from: https://en.m.wikipedia.org/wiki/Sanfilippo_syndrome. [Last accessed on 2019 Jun 20].
15. Meikle PJ, Grasby DJ, Dean CJ, Lang DL, Bockmann M, Whittle AM, *et al*. Newborn screening for lysosomal storage disorders. Mol Genet Metab 2006;88:307-14.
16. Fuller M, Tucker JN, Lang DL, Dean CJ, Fietz MJ, Meikle PJ, *et al*. Screening patients referred to a metabolic clinic for lysosomal storage disorders. J Med Genet 2011;48:422-5.
17. Wolfe BJ, Ghomashchi F, Kim T, Abam CA, Sadilek M, Jack R, *et al*. New substrates and enzyme assays for the detection of mucopolysaccharidosis III (Sanfilippo syndrome) Types A, B, C, and D by tandem mass spectrometry. Bioconjug Chem 2012;23:557-64.
18. Tomatsu S, Fujii T, Fukushi M, Oguma T, Shimada T, Maeda M, *et al*. Newborn screening and diagnosis of mucopolysaccharidoses. Mol Genet Metab 2013;110:42-53.
19. Germaine LD. Sanfilippo Syndrome (Mucopolysaccharidosis Type III); 2018. Available from: http://www.Medscape.com. [Last accessed on 2019 Jun 20].
20. Fedele AO. Sanfilippo syndrome: Causes, consequences, and treatments. Appl Clin Genet 2015;8:269-81.
21. Piotrowska E, Jakóbkiewicz-Banecka J, Barańska S, Tylki-Szymańska A, Czartoryska B, Wegrzyn A, *et al*. Genistein-mediated inhibition of glycosaminoglycan synthesis as a basis for gene expression-targeted isoflavone therapy for mucopolysaccharidoses. Eur J Hum Genet 2006;14:846-52.
22. Andrade F, Aldámiz-Echevarría L, Llarena M, Couce ML. Sanfilippo syndrome: Overall review. Pediatr Int 2015;57:331-8.
23. Tardieu M. Intracerebral administration of adeno-associated viral vector serotype rh.10 carrying human SGSH and SUMF1 cDNAs in children with mucopolysaccharidosis Type IIIA disease: Results of a phase I/II trial. Hum Gene Ther 2014;25:506-16.

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