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SANFILIPPO DISEASE TYPE B

A Case Report and Review of the Literature on Recent Advances in Bone Marrow Transplantation*

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A patient with enzymatically proven Sanfilippo disease type B is presented. This type of mucopolysaccharidosis results from deficient α-N-acetylglucosaminidase activity leading to defective degradation of heparan sulphate. As this disease is associated with high morbidity and mortality, different therapeutic approaches are under investigation. Bone marrow transplantation is among these new choices of management. The value of bone marrow transplantation in the mucopolysaccharidoses, especially in MPS IIIB, is discussed with a wide review of the literature. *Key words: Sanfilippo disease, mucopolysaccharidosis, bone marrow transplantation.*

Case Report

A four-and-one-half-year-old girl who had been diagnosed with mucopolysaccharidosis (MPS) in another hospital was admitted to Hacettepe University Children's Hospital, Department of Clinical Genetics. The family asked to be informed about the possibility of bone marrow transplantation (BMT) for this child.

The patient was the product of the eighth pregnancy of a couple with first degree consanguinity. Following three spontaneous abortions, the fourth child (Fig. 1, III-4) had been followed with the clinical diagnosis of mucopolysaccharidosis type III (MPS III; Sanfilippo syndrome) in another hospital. No enzymatic analysis for type determination had been performed. He apparently died at nine years of age as a result of progressive mental and motor deterioration. There is only one healthy child in the family (Fig. 1, III-5). The last two pregnancies were terminated on demand (Fig. 1).

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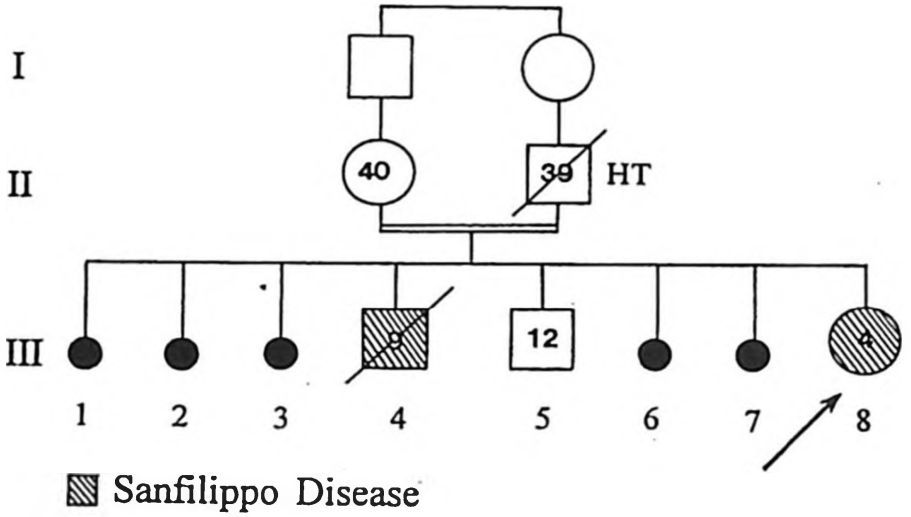

Fig. 1: The Pedigree

The prenatal and birth history of the patient were unremarkable. A sitting position was achieved at eight months of age, and she was reportedly able to walk by one year of age. She could also distinguish her mother. At one-and-a-half years of age, she was taken to another health center because of restlessness and sleep disturbances and a mildly protuberant abdomen. She was diagnosed with MPS III on the grounds of the family history, physical and x-ray findings coupled with a positive test for mucopolysaccharides in a spot urine sample. Genetic counselling was provided.

At the time of referral, her speech development was slow and poor. She was able to spell about 10-20 words. The parents complained of her restlessness and hyperkinesis. She was easily frightened and became aggressive in stressful situations. The family was now willing to learn whether the patient would benefit from BMT.

The patient weighed 20 kg (75^{th} - 90^{th} percentile). Her height was 108 cm (75^{th} - 90^{th} percentile) and head head circumference was 50.6 cm (within normal limits for age and sex; 49.9 ± 1.3 cm).

The physical examination revealed a mentally retarded patient with difficulty in cooperation. Her general condition was good. She had hirsutism and sparse hair growth. Prominent auriculae, coarse facial features with synophrys, anteverted nostrils, and an open mouth with a large tongue were observed. There was no clouding in her corneas and no joint limitation (Fig. 2). The liver was palpated two centimeters below the right costal arch.

The urinary excretion of mucopolysaccharides was 6.8 mg/dl in the spot urine sample. Her skeletal x-rays were consistent with mild dysostosis multiplex. A dense calvarium with increased diploe space, mildly oar-shaped ribs, and mild tapering at the proximal ends of the metacarpals were observed.

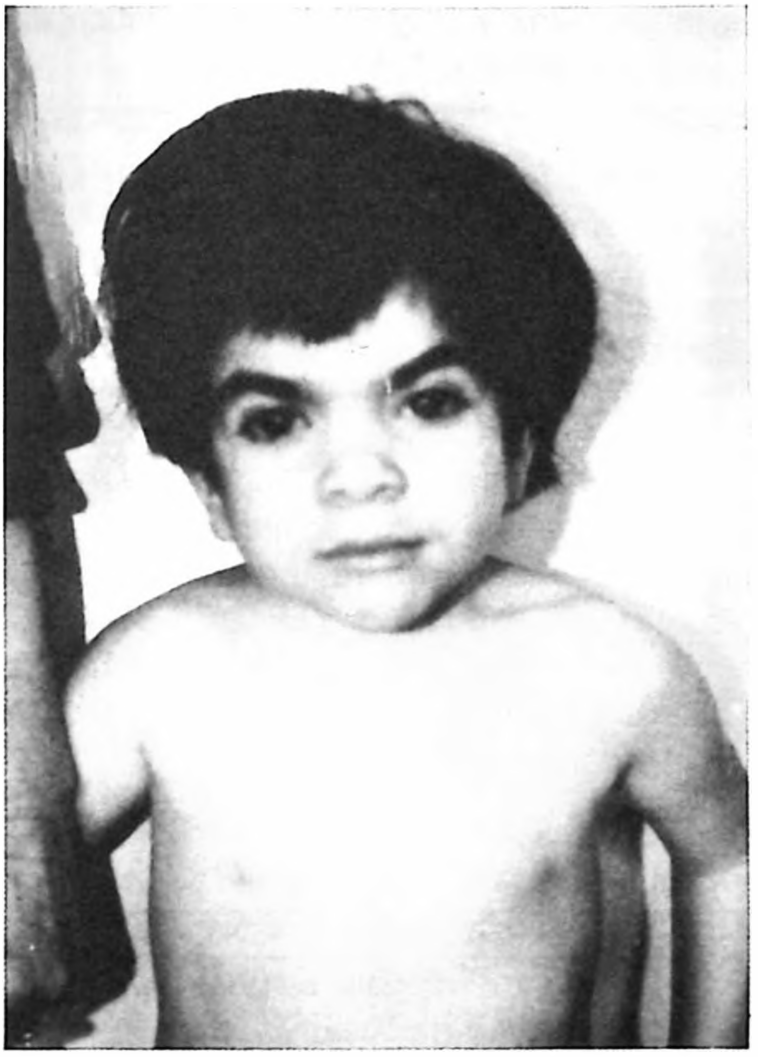

Fig. 2: The patient. Note the coarse facial features including the synophrys and the anteverted nostrils.

Fresh urine glycosaminoglycan analysis revealed large amounts of heparin and heparan sulphate, with heparan sulphate as the predominant fraction. This is typical for MPS III. Further studies on enzyme in leukocytes and plasma showed deficient o-N-acetylglucosaminidase activity. These results indicated a diagnosis of MPS IIIB.

Discussion

The mucopolysaccharidoses are a group of inherited disorders caused by a deficiency of specific lysosomal enzymes. The enzyme deficiency cause interference with cellular function because of excessive accumulation within the cells of partially degraded glycosaminoglycans, which are also excreted excessively in the urine. The type of glycosaminoglycan stored depends on the specific enzyme deficiency, and the classification of the group is now based on these deficiencies, rather than on clinical features[1]. The clinical presentations of patients with different types of MPS are summarized in Table I[1].

Table I: The Clinical Presentations of Patients with Different Types of MPS

Mode of Presentation	Type of MPS
Prominent dysmorphic features	MPS I, MPS II, MPS IIII
Behavior problems and dementia	MPS III
Bone dysplasia	MPS IV, MPS VI

In our patient the behavior problems related to mental retardation were more striking features when compared to the dysmorphic features. This was the initial point leading us to think in favor of MPS III. Sanfilippo syndrome is the most frequent of the mucopolysaccharidoses. The frequency is approximately 1:25,000[2]. The mode of inheritance is autosomal recessive. Excessive excretion of heparan sulphate in the urine is characteristic of this disorder[3,4]. Genetic heterogenetiy is present in Sanfilippo syndrome with the presence of four different enzyme deficiencies, in leukocytes, plasma, fibroblasts and other tissues, each of which forms a different subtype[2]. The enzymatic deficiencies in different subtypes of MPS III are demonstrated in Table II[4].

Table II: The Enzymatic Deficiencies in the Subtypes of MPS III (Sanfilippo Disease)

Subtype	Deficient Enzyme
Sanfilippo A	Heparan sulphate sulphatase
Sanfilippo B	N-acetyl-o-glucosaminidase
Sanfilippo C	Acetyl CoA: o-glucosaminide N-acetyltransferase
Sanfilippo D	N-acetyl-o-glucosamine-6-sulphate sulphatase

Recent studies point to great intertype and intratype variability in Sanfilippo syndrome[2]. This variability includes not only the phenotype of the patients but also the course of the disease. A study of 73 patients with Sanfilippo syndrome (types A, B and C) revealed that MPS IIIA, the most common subtype, was associated with an earlier onset, with more severe clinical manifestations and an earlier age at death. MPS IIIC was slightly less severe than MPS IIIA. The natural course of MPS IIIB seemed to be milder than that associated with types A and C.

On the other hand, an intratype variability was also observed in Sanfilippo syndrome type B, suggesting the existence of two allelic mutations[2]. Intrafamilial variability in Sanfilippo syndrome is another point of interest currently being investigated[2,5].

The mucopolysaccharidoses require a multidisciplinary approach to management involving not only pediatric subspecialties, such as cardiology and ophthalmology, but also other specialists including psychologists[1]. Today no definitively curative

treatment is available. Attempts are being made at enzyme replacement therapy[3, 4, 6, 7]. When the literature is reviewed on this issue, it is seen that in principle, BMT can be used to ameliorate any enzyme deficiency state, provided there is some reason to believe that enzyme-competent cells derived from the marrow or even enzyme released from them could be therapeutic[8]. Recently BMT has been used in proven states of enzyme deficiency (the lysosomal storage disorders). Severe combined immune deficiency, thalassemia and osteopetrosis are a few examples of genetic diseases that are correctable by BMT.

The mucopolysaccharidoses are also among the diseases that may be correctable by BMT[6]. But the use of BMT to treat inborn errors of metabolism involving the central nervous system (CNS) is still a subject of much controversy[3, 4, 6, 8]. Approximately 40 patients with Hurler's/Hunter's syndromes have been transplanted by the Westminster Hospital group using donors with a variety of histocompatibility relationships to the recipients. When using histocompatible donors, prompt donor lymphoid and hematopoietic engraftment have been observed with normalization of enzyme levels in the circulating leukocytes. However, marked improvement in the patient's non-CNS symptomatology would be of little clinical benefit unless it were paralleled by clinical improvement in the patient's CNS function. The long-term neurological outcome of these patients is still a subject of debate. Here the age at transplantation seems to be an important factor. Some patients who received transplantation at an early age (less than 18 months of age) are doing better than would have been predicted by their underlying disease, with some patients now in school with normal intellectual function; patients undergoing transplants at an older age appear to have had minimal benefit[6].

To the best of our knowledge, there are only three children with MPS IIIB who have received BMT and are reported in the medical literature. One of them is a girl whose age at transplant was 5.3 years and whose IQ was only 40. She continued to regress after BMT[3]. The other two patients were twins diagnosed with MPS IIIB at 18 months of age. They were clinically normal at that age and the diagnosis was made during the investigation of an elder sibling previously diagnosed with MPS IIIB. At the same time, another brother of theirs was similarly diagnosed. Nine-year follow-up post-transplant showed that neither twin was as handicapped as her untreated brothers were at the same age. Despite this, one of the twins was hyperactive and had behavioral problems characteristic of the disorder. On the other hand, both twins who showed functioning in the (low) average range according to Griffiths Scales prior to transplant, had a steady decline in cognitive development and had significant developmental delay. The authors find these results difficult to interpret, especially when taking into account the intrafamilial heterogeneic variation observed in MPS IIIB[3].

In conclusion, BMT does have a role in the management of the mucopolysaccharidoses. But in the forms with serious involvement of the brain, either there has not been any important difference in the final outcome of the neurologic deterioration or cases have not been followed long enough to permit an unequivocal conclusion to be drawn. As normal brain tissue is segregated from the circulation by the blood-brain barrier, it is doubtful that marrow-derived elements cross the barrier except under circumstances of injury or inflammation. Thus the direct transfer of enzyme to neurons has little chance of occurring. Considering the fact that BMT itself also entails considerable risks of morbidity and mortality, as well as a large commitment of medical, financial, psychosocial and other resources, it is still a controversial management for mucopolysaccharidoses with CNS involvement. Still, since the number of cases is not many, the disease is associated with an unacceptable morbidity and there is no effective alternative therapy, BMT may be applied to MPS IIIB patients who are as yet clinically unaffected. Providing a compatible related donor and informing the parents of the risks of both the procedure and the prognosis of the untreated disease, are still the most important issues while making the decision. For all these reasons, our patient was not thought to be a suitable candidate for this procedure. We believe that the answers may be found after long-term follow-up of a sufficient number of cases, and investigations at the molecular level will add a lot to our understanding of not only the heterogeneity in the natural course, but also of patterns of improvement after BMT. Therefore we emphasize the importance of proper genetic counselling and attempts at prenatal diagnosis for selected families whose future siblings are at risk of carrying this disorder, which is still practically untreatable.

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