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# A CASE REPORT OF SANFILIPPO SYNDROME (MUCOPOLYSACCHARIDOSIS III) PRESENTING AS RECURRENT RESPIRATORY INFECTIONS WITH GROWTH FAILURE AND NOCTURNAL HYPERACTIVITY

**Paediatrics**

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## ABSTRACT

Mucopolysaccharidosis III (MPS III) or Sanfilippo disease is a rare error of Glycosaminoglycan (GAG) metabolism resulting from the absence of any of the four enzymes that metabolise Heparan Sulphate (HS).
We report a case of MPS III presenting with recurrent chest infections, global developmental delay, growth failure and nocturnal hyperactivity.
A high threshold of suspicion for both the minimal somatic signs as well as typical behavioural changes of MPS III need to be maintained in clinical practice in conjunction with other less common presenting features. The role of anthropometric assessment, ophthalmological assessment, screening of urine for GAG excretion, and neuroimaging to determine extent of neurological involvement and prognosticating severity is described with review of relevant literature. A thorough clinical examination with history taking is important in any child with developmental delays, and organomegaly with dysmorphism can point the finger at a metabolic or storage disorder that can otherwise go unnoticed.

## KEYWORDS

Sanfilippo syndrome; Nocturnal hyperactivity; Growth failure; recurrent respiratory infections

## INTRODUCTION

Mucopolysaccharidoses (MPS) are autosomal recessive disorders, counted among 41 rare inherited lysosomal storage disorders (LSDs). They are due to deficiency in enzymes which degrade Glycosaminoglycans (GAGs). A high prevalence of LSDs may be seen in certain populations, up to 1 per 7700 live births for all LSDs as per a study conducted in Australia in the period 1980-1996 [1]. Among all LSDs, MPS alone were found in 1 in 25,000 births, reported in a Northern Irish epidemiological study [2]. However, it is not possible to estimate the true burden of MPS in the population as often mild forms go unnoticed or misdiagnosed. In South Asia, the MPS continue to be under-reported. The severity and extent of involvement of different organ systems varies not only among the individual mucopolysaccharidoses, but also within a single type, with varying degrees of affection seen even among siblings. All of these pose a significant challenge to the clinician in order to identify and diagnose MPS [1, 2].

Mucopolysaccharidosis III (MPS III) or Sanfilippo disease (estimated at 1 in 70,000 live births [3, 4]) is a syndrome resulting from the absence of any of the following four enzymes in order of the sequence of which they act: a) heparan N-sulphatase encoded by SGSH gene, b) α-N- acetyl glucosaminidase or NAGLU, c) acetyl CoA: α-glucosaminide-N-acetyltransferase, encoded by HGSNAT gene, and d) N-acetyl glucosamine 6-sulphatase, encoded by GNS gene, to break down GAG heparan sulphate. If undegraded or partially degraded, heparan sulphate accumulates in lysosomes and is excreted via urine, causing MPS III type A, B, C or D respectively and leading to the typical clinical features. [4,5]

## CASE REPORT

A 3 years, 3-month-old male child presented to the Paediatrics out-patient department with a complaint of repeated respiratory infections. The child had been born to non-consanguineous Bangladeshi parents with a history of maternal polyhydramnios and possible delayed cry at birth, and the child required hospitalisation for pneumonia with sepsis at 2 months of age. This was followed by recurrent chest and ear infections.

He was diagnosed with Hypoxic Ischaemic Encephalopathy type II on basis of his delayed cry, which was assumed to be the likely cause behind his delayed walking. He had previously undergone a neurological work-up due to a background of global developmental delay, inappropriate growth and behavioural problems. CT scan and MRI Brain reports were unremarkable. From the age of 2 years the child started demonstrating temper tantrums and nocturnal hyperactivity, associated with nocturnal polyuria.

On examination the child had coarse facies with low-set ears. There was mild hepatomegaly but no splenomegaly. The anterior fontanelle was still open; there had been motor delay, but he now demonstrated an independent gait, and he had delayed speech with few words only.

Parents expressed concerns over delayed growth, and anthropometric measurements confirmed the child to be less than 1st centile for weight (11 kg) and below 1st centile for height (88 cm) indicating a gross growth stunting. The BMI was 14.2 (3.7th centile).

To investigate his poor growth, thyroid profile, serum vitamin D and CPK levels were tested and were within limits. A general work-up was normal and revealed no organic cause for polyuria.

MRI Brain was repeated and showed hyperintense T2 weighted bilateral parieto-occipital regions, suggesting delayed myelination. There was poorly developed corpus callosum in the region of splenium and rostrum but was otherwise unremarkable and revealed no features suggestive of hypoxic ischaemic encephalopathy. Ophthalmoscopic examination showed tessellated fundus possibly due to myopia, but otherwise normal with a clear cornea and healthy retina. An echocardiogram was normal.

The child had previously been investigated according to parental concerns for his individual complaints only, visiting multiple specialsts without any conclusion, and after taking into account the entire symptom complex, especially in light of the dysmorphic facies, hepatomegaly, delayed milestones, hyperactivity, disturbed sleep patterns, stunted growth and repeated ear infection, the child was investigated for Mucopolysaccharidoses. Urine GAG level by one-dimensional electrophoresis method revealed a high heparan sulphate and a GAG: Creatinine ratio of 17.3. Chrondroitan sulphate and dermatan sulphate were only mildly raised. This indicated a diagnosis of Sanfilippo disease (MPS III) showing onset of progressive Central Nervous System (CNS) changes, mild organomegaly, global delay in milestones, repeated respiratory infections and short stature.

## DISCUSSION

Although characteristic coarse facies, and multiple organ involvement (hepatosplenomegaly, neurological involvement, and skeletal and joint abnormalities including short stature) may be reasons for initial presentation, all four types of Sanfilippo syndrome commonly first present with sleep disorders and aggressive behaviour, as is seen in this child. All types demonstrate intellectual disability of different degrees, progressive loss of pre-acquired skills, and may have hearing loss [5]. San Filippo disease presenting with seizures, masquerading as febrile convulsions, has been reported [6]. A history of delay in crawling or walking is usually present, and an unsteady gait progressing to gradual inability to walk may be seen if the child presents well into late childhood [5]. There may be associated heart abnormalities.

The clinical course of Sanfilippo syndrome is three-staged, based on gradual decline in CNS function; the first is at 1-4 years of age with developmental delay following a short phase of normal development. This is followed by approximately 3-4 years of behavioural problems and progressive cognitive deterioration progressing to profound loss of mental capacity and intractable hyperactivity; in the above reported case the child appears to be entering this stage. The third and final phase involves attenuation of aggressive behaviour with withdrawal from the external environment, and onset of profound motor deficits including dysphagia and spasticity [7]. Most affected individuals live till the end of the second or beginning of the third decade and survival into the fourth decade is rare.

According to Muschol et al, subjects with MPS III in Germany [8] showed deceleration of growth velocity after the ages of 4.5 years for girls and 5 years for boys with an initial rapid growth rate in the first year of life. Males show as many as 5 growth spurts between 5-17 years, and females 1, at 9 years, with a growth velocity comparatively less than the normal population. Phenotypic severity clinically correlates with final adult height attained for both sexes, and is lower than expected. Mean BMI in both boys and girls is higher than normal [9]. The reason for short stature and growth defect in MPS III is unclear; hypotheses suggest that lysosomal GAG deposition triggers inflammatory mediators, apoptosis, autophagy, alters signal transduction pathways and disrupts extracellular matrix. Growth hormone/IGF-1 resistance, and chondrocyte organization defects in the growth plate and cortical bone framework has also been implicated [8].

Retinopathy, including retinal dysfunction and degeneration, is the characteristic ocular finding in Sanfilippo syndrome and the time of onset depends on the severity of the phenotype [10]; it is due to Heparan sulphate deposition within the retinal pigment epithelium and photoreceptor matrix. Early fundoscopic changes include arteriolar attenuation, and later marked pigmentary changes set in. Night-blindness and reduced peripheral vision [11] are reported. Refractive errors, including myopic changes may be present as seen in this case, as described by Lin et al [12]. Corneal opacification is not commonly associated with MPS III. However, taking neurocognitive decline of patients into consideration, the merits of active ophthalmological management varies according to individual cases.

Unlike other MPS, airway obstruction in MPS III is minimal, but chest and middle ear infections, as was present in this case, along with diarrheal diseases are frequent. Lavery et al found that respiratory tract infections, especially pneumonia, is in children with Sanfilippo syndrome types A and B, the commonest cause of death [13].

Prenatal diagnosis using amniocentesis and chorionic villus sampling involves DNA studies on tissue samples from the placenta proving useful in families with a previously affected child [14]. He et al reports that fluorometric assay in case of MPSIII type C applied to amniocytes, chorionic villi and foetal fibroblasts using 4.methylumbelliferyl β.D.glucosaminide as substrate has successfully diagnosed the disease [15]. An Indian study proposes high amniotic fluid GAGs excreted by foetal kidneys as a possible rapid and cost-effective avenue for MPS prenatal diagnosis in advanced pregnancies in cases of MPS II and VII, but this has not yet been studied to screen for MPS III [16].

Urine analysis to detect excessive levels of mucopolysaccharides are quantitative tests which use urine creatinine concentration and age as reference, thus reducing the incidence of both false negatives and false positives. They range from simple direct screening of urine for GAGs to methods that purify urinary GAGs using precipitation techniques before analysis. The cetylpyridinium chloride (CPC) test has been used as a convenient and inexpensive tool to distinguish MPS III from other MPS [17]. These quantitative methods remain the mainstay in diagnosis of MPS III as in seen in this case. However according to Piraud et al, quantitative GAG excretion alone cannot rule out a diagnosis of MPS, and qualitative analysis of the type of GAG as well as oligosaccharide screening is recommended [18]. Mutational analysis confirms the diagnosis which is imperative for management as well as family screening and genetic counselling.

Magnetic resonance imaging (MRI) is used to identify brain and spinal cord abnormalities, exclude other metabolic diseases, and aids monitoring and evaluation of treatment response. In Sanfilippo type B, like MPS II A, there are focal or confluent areas of T1 hypo-intensity and T2-FLAIR hyperintensity in the white matter suggesting incomplete myelination and GAG infiltration as observed in this case. These findings correspond to high incidence of mental retardation in these forms of disease [19, 20]. Cortical atrophy is marked in all MPS III and probably the result of neuronal death and gliosis induced by accumulation of GAGs [21, 22] and probably found in the later stages of the disease. Corpus callosum thinning is seen possibly secondary to ventricular dilation and enlarged periventricular septum in types A and B [22]. In the above case, cortical atrophy, delayed myelination and corpus callosum involvement have been described in the child. .

Sanfilippo disease remains untreatable, and symptomatic treatment and supportive care is the mainstay. Among the therapies under research is gene therapy using viral vectors, which allows for some degree of lysosomal enzymatic secretions, and may lead to reversal of somatic changes, thus being a promising answer to the treatment of other MPS. However, it has failed so far in Sanfilippo disease, as the major system to be involved is the Central Nervous System, and the enzymes, even if high in serum concentration, fail to cross the blood-brain barrier. A 2019 study by Marco et al [23] proposes Adeno-associated virus (AAV) vector mediated gene transfer either by direct Cerebrospinal fluid (CSF) delivery or multiple-site intra-parenchymal injections. In another study, MPS IIIA patients given direct to CNS gene therapy showed good tolerance to a first-generation AAV gene therapy (with SAF301), and second-generation optimized gene therapy is under trial [24]. Hematopoietic stem cell gene therapy (HSCGT) is another promising strategy as it too bypasses the blood-brain barrier; neurological improvement was seen in MPS IIIA after HSCGT via a lentiviral vector encoding the SGSH gene in pre-clinical studies [25].

## CONCLUSION

Sanfilippo syndrome has been studied relatively little, and till now the pathophysiology at the cellular level that underlies the behavioural disturbances and neurodegeneration is not completely understood. In India and its neighbouring countries in South Asia, the reporting of LSDs such as MPS remains low, with limited access to tertiary care centres and lack of awareness about genetic disorders. The true size of the problem in the region is unexplored and it's clinical and genetic spectrum ill-defined due to an absence of large-scale epidemiological data in regional medical literature. There is a need for screening, genetic analysis and detailed reporting of suspected cases to further our understanding of the disease. A high threshold of suspicion to appreciate mild somatic symptoms as well as typical behavioural changes needs to be maintained in clinical practice. It is important to ensure that organic causes of hyperactivity, speech delay, and behavioural issues and effectively ruled out.

We have reported a case of a child with Sanfilippo disease diagnosed at the start of possible neurocognitive decline. The identification and screening of suspected cases by enzyme assay, estimating the extent of central nervous system involvement via proper neuroimaging and confirmation by mutational analysis to determine type of MPS III is imperative. Although largely untreatable, diagnosis is especially required to aid genetic counselling for future issues in families with affected children.

## ABBREVIATIONS-

MPS: Mucopolysaccharidoses
LSD: Lysosomal Storage DIsorders

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