

Case Report

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A 7-year-old boy with progressive developmental regression: A case of Sanfilippo disease

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Abstract

We present the case of a 7-year-old boy with a history of aggressive behavior, speech delay and progressive neurodevelopmental regression. Mucopolysaccharidosis was suspected based on skeletal and behavioral symptoms and confirmed by whole exome sequencing.

Keywords: Sanfilippo disease, Neurodevelopmental regression, Mucopolysaccharides

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Clinical Description

Our patient was a 7-year-old boy who presented with inability to walk. He had a history of delayed speech development, developmental regression, aggressive behavior and hyperactivity who was being treated as ADHD and autism spectrum disorder. Starting a year before admission he had begun having difficulty standing up from a sitting position. Dysphagia and drooling had been an issue for 14 days and for a week before admission he had developed a disability to walk and would fall down repeatedly.

He had a past history of cyanosis and apnea at birth for which he had been hospitalized. Head circumference had been slightly greater than normal in infancy. He had not begun speaking until he was 3 years old and even with speech therapy could speak only a few words. His motor and verbal skills had diminished even further since he was 5 years old and severe aggressive behavior had been in a problem in the course of speech and occupational therapy. He did not have a history of seizures but had developed jerky leg movements. For his behavioral problems he had been started on Haloperidol and Trihexyphenidyl since 2 months before admission.

His parents were first cousins. He was their first child. They had since had a miscarriage at 16 weeks of pregnancy and also had a healthy 4-month old boy. There was a family history of delayed speech development in patient's cousins.

On admission the patient was awake but would not communicate with the examiner. He had a blood pressure of 120/80, PR=100, RR=30 and T=37.5°C. He had rather coarse facial features (which were similar to his father's), oral candidia-



Fig. 1. Coarse facial features

sis and copious muco-purulent respiratory secretions. There was no organomegaly. On neurological exam cranial nerves were normal and gag reflex was intact. Limbs were spastic with exaggerated deep tendon reflexes and occasional jerky movements. There seemed to be no sensory deficit.

In the course of the next few days the patient became progressively lethargic and had seizures which were controlled with Phenytoin and Diazepam. His oropharyngeal function progressively worsened, resulting in an inability to eat and frequent aspiration which ultimately resulted in a percutaneous gastrostomy being placed. His respiratory infection proved challenging to control. He also developed splenomegaly, anemia and thrombocytopenia.

Cerebrospinal fluid analysis and culture were normal. Brain MRI showed generalized brain atrophy both deep and cortical and a widening of subarachnoid spaces. Cervical and thoracolumbar

MRI were performed that showed disc protrusion in L4-L5, dural ectasia in distal lumbar spine, disc bulging in other lumbar levels, loss of signal in T12-L1 disc due to dehydration and degenerative joint changes and bone marrow edema in T12-L1 endplate. EMG-NCV was compatible with active denervation of most upper and lower limb myotomes suggestive of generalized motor neurogenic processes. EEG was mildly abnormal.

His coarse facies, skeletal changes, progressive motor, speech and behavioral regression and consanguineous marriage between his parents suggested a neurodegenerative disease. Whole exome sequencing provided the diagnosis of Mucopolysaccharidosis Type IIIA. Figure 1 is picture of the patient through childhood period. Figure 2 is spinal MRI of the patient with structural abnormalities in vertebral bodies.

Discussion

The mucopolysaccharidoses are a heterogeneous group of disorders resulting from deficiencies of the various lysosomal enzymes involved in the sequential degradation of glycosaminoglycans and consequently disrupting their diverse biochemical and physiological roles. Although each MPS subtype is due to a distinct enzyme deficiency there is significant overlap in the non-neurologic manifestations across the individual diagnostic entities. The two most characteristic manifestations are coarse facial features and dysostosis multiplex (1).

Developmental regression is a feature of most but not all MPS subtypes. The accumulation of heparin sulfate and the secondary storage of gangliosides in neurons may be partly responsible for the cerebral dysfunction (2).

The Sanfilippo syndrome (or MPS III) is an autosomal recessive disorder, caused by a deficiency in the degradation of the glycosaminoglycan heparan sulfate. Based on the enzyme deficiency, it is further classified into four different subtypes, MPS IIIA, B, C, and D (3).

The clinical course of MPS III can be divided into three phases (2-4). After an initial normal development the first phase begins with a developmental delay between 1 and 4 years of age. Some patients have ear disease and will fail hearing tests which is the usual reason given initially for the speech delay. Abundant hair and hirsutism are often noted (4). The second phase occurs around 3-4 years and is characterized by severe behavioral problems and progressive mental deterioration ultimately leading to severe dementia. Sleep disturbance that is resistant to usual hypnotics is hard to treat and almost a universal problem for these



Fig. 2. Spinal MRI showing structural abnormalities in vertebral bodies

patients (5). In the third and final stage. Behavioural problems slowly disappear as patients lose locomotion. Swallowing difficulties, spasticity and epilepsy emerge. Patients eventually regress to a fully bedridden and vegetative state, and they usually die at the end of the second or beginning of the third decade of life (3, 4, 6).

It is clear that MPS III is a diagnostic challenge, particularly in the early stages and in the absence of a family history of the disease (6). This is partly due to the absence of obvious coarse facial characteristics of other MPS syndromes and typically results in long delays in diagnosis (2, 3, 6). These children, like our case, are often misdiagnosed with autism or pervasive developmental disorder which may subject them to more invasive testing, dietary restrictions or even unproven alternative therapies that eventually prove unnecessary or perhaps harmful (6, 7).

Conflicts of interest: None declared.

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