Molecular Genetics and Metabolism Reports 40 (2024) 101113

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Case Report

Initiation of fluoxetine in a pediatric patient with Mucopolysaccharidosis IIIA: Early observations

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ARTICLE INFO

Keywords:
Mucopolysaccharidosis
Sanfilippo syndrome
MPS IIIA
Fluoxetine
Glycosaminoglycan
Pediatric

ABSTRACT

Fluoxetine has been identified as a potential treatment for mucopolysaccharidosis IIIA (MPS IIIA), a debilitating and progressive lysosomal storage disorder for which no treatments are approved. In the MPS IIIA mouse model, fluoxetine decreases the accumulation of glycosaminoglycans and aggregated autophagic substrates, reducing inflammation, and slowing cognitive deterioration. [1] We treated a single patient, 6 years old, under off-label prescription of fluoxetine, a selective serotonin reuptake inhibitor (SSRI). The primary endpoint was safety. Secondary exploratory assessments included urine quantitative heparan sulfate. Fluoxetine was well-tolerated in this patient and the patient continued treatment following the 12-month monitoring period. The patient experienced an increase in daytime somnolence which resolved with rescheduling fluoxetine administration to bedtime. Quantitative heparan sulfate levels remained elevated during treatment. Parents reported improved sleep latency time and less nighttime waking. These findings support general tolerability and further study of fluoxetine as a potential therapy for MPS IIIA.

1. Introduction

Mucopolysaccharidosis IIIA (MPS IIIA, Sanfilippo A syndrome), is a rare, inherited lysosomal storage disorder in which the deficiency of SGSH enzyme (sulfamidase, N-sulfoglucosamine sulfohydrolase) causes accumulation of glycosaminoglycans (GAG), specifically heparan sulfate, in the central nervous system [2,3]. Although MPS IIIA is the most common subtype, there are four autosomal recessive subtypes of MPS III (types A, B, C, D) with estimated combined prevalence between 1:50,000 and 1:250,000 [2]. Accumulation of GAGs leads to progressive, debilitating neurological disease, with early developmental plateau followed by regression resulting in profound cognitive impairment and premature death (often in the teenage years) due to overwhelming neurological devastation [4–6].

Currently, no treatment has been approved for MPS IIIA. Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) with indications including depression and obsessive compulsive disorder in pediatric patients [7]. Dosage recommendations range from 10 mg to 40 mg PO once daily, titrating to target dose while monitoring for efficacy and side effects [7]. Fluoxetine is generally well-tolerated in pediatric or adolescent patients, but side effects may include sedation, insomnia, disinhibition, agitation and/or hyperactivity [8].

In vivo, fluoxetine ameliorates somatic and brain pathology in a mouse model of MPS IIIA by decreasing the accumulation of glycosaminoglycans and aggregated autophagic substrates (including p62 and p-129-α-synuclein), reducing inflammation, and slowing cognitive deterioration. [1] *In vitro* studies demonstrated activation of transcription factor EB (TFEB) and upregulation of TFEB target genes, as well as a reduction in accumulation of HS in the lysosome of fluoxetine-treated MPS IIIA mouse embryonic fibroblasts [1]. Quantification of GAG in the fluoxetine-treated murine model was performed on liver and brain tissues [1]. This proof-of-concept work suggests that fluoxetine may reduce GAG storage in patients with MPS IIIA.

2. Methods

The patient received 2.5 mg fluoxetine PO once daily, increasing at two-week intervals to 5 mg PO once daily, followed by 10 mg PO once daily, until reaching dose of 20 mg PO once daily. Quantitative urine heparan sulfate (HS) levels were analyzed *via* Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) at Mayo Clinic Laboratories. Per their testing standards, the normal range for urine HS in a patient

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https://doi.org/10.1016/j.ymgmr.2024.101113
Received 22 January 2024; Received in revised form 24 June 2024; Accepted 25 June 2024

>/= 5 years is </= 0.25 mg/mmol creatinine. Urine HS was measured prior to initiating fluoxetine with repeated measurements during titration and maintenance of therapy. After approximately 5 months, the patient tolerated a final dose increase to fluoxetine 30 mg PO once daily.

3. Results

This patient was selected due to parent interest in fluoxetine therapy for disease modification. Due to positive family history, she was diagnosed in infancy with confirmation of elevated urine GAG, decreased SGSH activity, and pathogenic variants in SGSH gene (p.F225L and p.R245H). She has been followed in our clinic since infancy and displayed the classical phenotype during early childhood. At the start of treatment, her vocabulary was declining, and her hyperactivity was worsening, but she was maintaining her mobility and feeding skills. Over 12 months of treatment monitoring, fluoxetine was well tolerated with no notable safety concerns. The patient experienced an initial increase in daytime somnolence which resolved with rescheduling fluoxetine administration to bedtime. Parents reported the patient fell asleep faster and slept through the night during treatment, although she had minimal difficulty with falling asleep prior to treatment. Quantitative urine heparan sulfate (HS) analysis was performed prior to initiation of fluoxetine therapy and repeated multiple times during dose escalation and maintenance (Fig. 1). Quantitative urine HS levels remained elevated during the treatment monitoring period.

4. Discussion

MPS IIIA is a debilitating, progressive neurodegenerative disorder resulting in profound neurological impairment and premature death, with no currently available treatments. Clinical signs and symptoms include developmental delay, speech delay, sleep or behavior problems, and developmental regression. Progressive neurological disease results in patients eventually losing the ability to speak, walk, and eat or drink independently. Patients may also suffer seizures and may persist in a vegetative state for years before premature death.

To date, no clinical or preclinical studies have evaluated the effect of fluoxetine on urine GAG levels. Given the proposed mechanism of action by which fluoxetine ameliorates GAG storage in the murine model (enhancing excretion, not breakdown), it is challenging to determine whether urine GAG levels would be expected to increase or decrease. It is possible that a higher dose of fluoxetine would be required to affect urine GAG levels in a pediatric patient, although the equivalent dosage administered in the murine model would be well above the recommended range in a pediatric patient. In this patient, urine HS levels remained above the normal range during treatment. Limited data are available about the stability of urine HS levels in individuals with MPS IIIA over time; therefore, the significance of the fluctuations in urine HS during the monitoring period is unclear. Due to the requirement for anesthesia and invasive nature of the procedure, the providers declined to perform lumbar puncture for CSF collection prior to or during treatment.

Positive effects on sleep initiation and maintenance were observed by parents. Although these effects may be a side effect of fluoxetine rather than improvement in the underlying pathophysiology of disease, improvement in sleep patterns would be considered favorable in the MPS IIIA population. No defined behavioral or developmental assessments were completed during the treatment monitoring period.

Considering the lack of available treatments for this devastating disorder, the positive results of the proof-of-concept study of fluoxetine in an MPS IIIA mouse model, and the safety and tolerability of fluoxetine in a pediatric patient with MPS IIIA, further study of fluoxetine as an adjunct therapy for MPS IIIA is warranted.

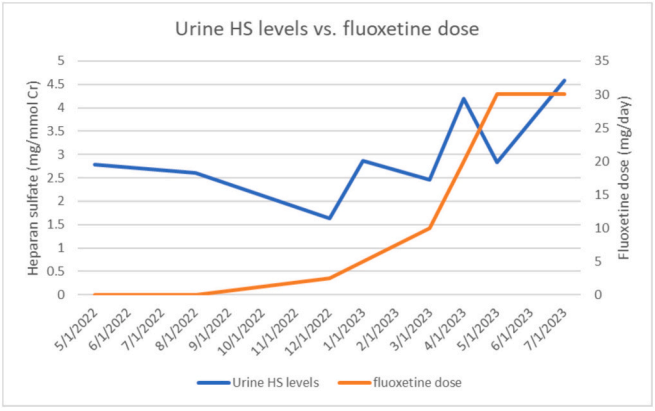

Fig. 1. Urine heparan sulfate (HS) levels remained above the normal range during the fluoxetine administration period. The significance of fluctuations in urine HS levels is unclear due to limited data about the stability of urine HS levels in individuals with MPS IIIA over time.

CRediT authorship contribution statement

Lindsay Torrice: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Conceptualization. **Elizabeth Jalazo:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

All authors declare that they have no conflict of interest.

Data availability

Data will be made available on request.

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