CASE REPORT

Mucopolysaccharidosis type IIIB (MPS IIIB) masquerading as a behavioural disorder

Jacqueline Brady,¹ Aditi Trehan,¹ Dennis Landis,² Camilo Toro²

¹Office of the Clinical Director, NHGRI/NIH, Bethesda, Maryland, USA
²Undiagnosed Diseases Program, NHGRI/NIH, Bethesda, Maryland, USA

Correspondence to
 Dr Camilo Toro,
 toroc@mail.nih.gov

SUMMARY

Inborn errors of metabolism (IEMs) that manifest primarily as psychiatric and behavioural symptoms in childhood are often mistaken for idiopathic primary psychiatric disorders. The pathophysiological basis of these symptoms may be overlooked until later in the disease course when neurological deficits become dominant; this results in a significant delay in establishing a proper diagnosis. To illustrate this, we describe two siblings who presented with behavioural issues and mild learning disabilities in childhood, and were consequently given multiple psychiatric diagnoses. In early adulthood, however, they manifested a rapid cognitive decline. Subsequent cranial MRI imaging revealed progressive brain iron accumulation in deep brain nuclei. Whole exome sequencing and biochemical investigation confirmed the diagnosis of mucopolysaccharidosis type IIIB. Their long diagnostic odyssey illustrates the importance of considering IEMs when assessing individuals with behavioural abnormalities and cognitive impairment.

BACKGROUND

Psychiatric symptoms, such as altered mood, attention deficits and behavioural disturbances are fairly prevalent in childhood and adolescence.^{1 2} Most often, young patients who present with these symptoms are given a primary psychiatric diagnosis and treated through a variety of behavioural interventions and pharmacological means. In a small subset of cases, however, the observed symptoms represent manifestations of an inborn error of metabolism (IEM). Examples of well-known IEMs that present with primary psychiatric symptoms include Wilson's disease, adrenoleukodystrophy (ALD), metachromatic leukodystrophy (MLD), acute intermittent porphyria (AIP) and several lysosomal storage disorders (LSDs).^{3 4} Based on clinical presentation alone, it can be difficult to distinguish these disorders from primary psychiatric and behavioural diagnoses, especially early in the course of the disease.

To highlight this difficult clinical scenario, we report the cases of two siblings presenting with disruptive attention and behavioural issues as well as mild learning disabilities in early childhood. Both patients were given a variety of psychiatric diagnoses, and both received therapeutic intervention focused primarily on attaining acceptable behaviour. It was not until they experienced significant cognitive decline in adolescence and early adulthood that the diagnosis of mucopolysaccharidosis type IIIB (MPS IIIB) was established as the cause of

their early behavioural phenotype. Herein, we review the clinical spectrum of MPS IIIB, draw attention to elements in the clinical history that should heighten suspicion for this diagnosis, and report MRI findings suggesting that MPS IIIB should be considered in the differential diagnosis of patients with neurodegeneration with brain iron accumulation (NBIA).

CASE PRESENTATION

Patient 1 was a 26-year-old Caucasian female who presented to the Undiagnosed Diseases Program at the National Institutes of Health (NIH) with progressive cognitive decline resulting in the inability to live and function independently. She was the second child born to non-consanguineous healthy parents. Her family history was notable for a similarly affected older sister (patient 2). Patient 1 was delivered by elective caesarean section following an uncomplicated pregnancy. Her birth weight was 9 lbs 1 oz. She had normal early development. She walked and uttered single words by age 1 year and spoke in sentences by age 2 years. She was toilet trained and able to dress unassisted by age 3 years.

In preschool, she had subtle fine motor coordination issues. In kindergarten, she exhibited impulsive behaviour, inability to focus and hyperactivity. Consequently, she was diagnosed with attention deficit disorder (ADD) and treated with methylphenidate. In first grade, she struggled with math and reading, and ultimately required special education services. In the ensuing years, she exhibited increased impulsivity, inattentiveness, episodic temper outbursts, oppositional behaviour, social immaturity and phobias. A comprehensive evaluation at age 8 described her as verbal, cooperative and impulsive with an estimated full scale IQ of 92. She was given the primary diagnoses of ADD, pervasive developmental disorder (PDD) and oppositional defiant disorder (ODD). Neither her behaviour nor her learning disability significantly improved with medical therapy.

From age 9 to 14, her full scale IQ declined and then stabilised at 62 until age 21. During this time, all other parameters remained fairly stable. She was verbally fluent, but had atypical grammar and syntax. She was able to perform most self-care activities, including the preparation of simple meals with family supervision. By age 20, she began to experience a rapid progressive cognitive decline, after which she became incontinent and required constant supervision. She eventually transitioned to a group home for 24-h care. Over the next 2 years, she lost conversational skills and her ability to

To cite: Brady J, Trehan A, Landis D, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-009592

perform most activities of daily life, such as dressing, brushing her teeth and toileting.

Patient 2 was the 31-year-old sister of patient 1. She was born by elective caesarean section secondary to a diagnosis of placenta praevia. In early childhood, she presented with severe psychiatric symptoms and mild intellectual disability. She exhibited irritability, aggressive behaviour, inattention and auditory hallucinations. Some of her symptoms were successfully managed with antipsychotic medications. Similarly to her sister, patient 2 experienced a relatively rapid cognitive decline in her early 20s, which rendered her nearly mute and unresponsive to verbal commands. She was medically unable to travel to the NIH for evaluation.

INVESTIGATIONS

The evaluation of patient 1 in early childhood included a karyotype, *FMR1* mutation analysis, urine organic acid and plasma amino acid profiles, and thyroid function, all of which were normal. Her physical examination at age 8 indicated her height, weight and head circumference were >95th percentile. She had no gross dysmorphic features, no hepatosplenomegaly and mild joint hyperextensibility. She had mild dyspraxia and subtle difficulty with rapid rhythmic and alternating movements. Her ECG was within normal limits. Her EEG lacked epileptiform activity. At age 12, an MRI of the brain without contrast was normal. Following her rapid cognitive decline in her early 20s, she was evaluated by a behavioural neurologist who found mild cerebellar signs, hyper-reflexia and ankle clonus. Behavioural assessment revealed a combination of apathy, disinhibition and apraxia. Her language and verbal competency were at the level of a 5-year-old; her verbal utterances tended to be stereotyped and echolalic.

She was re-evaluated at the NIH Undiagnosed Diseases Program at the age of 25, and although alert and cooperative, her spontaneous speech was limited to two or three words. Her comprehension, reading and writing were also markedly impaired. She was able to distinguish tokens based on colour, but not based on size or shape. She was able to name numbers and letters presented on cue cards, but she could not read words like 'In' or 'My'. When asked to write her name or specific letters on a piece of paper, she simply drew circles. Overall, her performance indicated a profound decline in her cognitive abilities when compared to prior testing. Physical examination revealed easy fatigability, hyperextensible joints and severe pes planus. She had patulous lower lips, a narrow palate, long and gracile fingers, and long narrow feet. Abdominal ultrasound indicated hepatomegaly without splenomegaly. Neurological examination found her to be hypotonic with normal deep tendon reflexes and no clonus.

Biochemical and haematological investigations were normal apart from an elevated serum iron of 180 µg/dl (normal range 50–150) and a low 24-h urine copper at 6 µg (normal range 15–16). A serum N-glycan panel revealed hyposialylation of N-linked protein glycosylation, but normal transferrin isoelectric focusing. Urinary oligosaccharide and glycan screening showed marked elevation of several small fucosylated oligosaccharides, as well as mild elevation of sialylated and galactosylated oligosaccharides in a pattern suggestive of possible lysosomal dysfunction. A lysosomal enzyme screening panel indicated normal enzyme activity for α- and β-mannosidase, hexosaminidase A, β-glucuronidase, α- and β-galactosidase, α-fucosidase, β-glucosidase, α-iduronidase, arylsulfatase A and B, and acid α-glucosidase.

Figure 1 Axial FLAIR images (T=3.0) obtained for patient 1 at age 25 across the lateral ventricles, globus pallidus and thalamus, substantia nigra and red nucleus, and dentate nucleus are shown in A–D, respectively. Additional T2 and T2* GRE images across the globus pallidus are depicted in E and F. Areas of decreased signal intensity in the various deep brain nuclei are indicative of increased iron deposition.

On a repeat MRI, there was mild progression of cerebral atrophy with greater involvement of the parietal lobe, and subtle posterior periventricular white matter signal abnormalities. More notable, however, was the presence of T2 signal hypointensity suggestive of increased iron deposition primarily within the globus pallidus but also the caudate, posterior aspects of the thalamus (pulvinar region), substantia nigra, and red and dentate nuclei (figure 1). Retrospective analysis of an MRI study conducted at age 23 suggested these same findings but to a lesser degree. Although patient 2 was not evaluated by the NIH Undiagnosed Diseases Program, earlier studies from ages 24 and 28 revealed similar findings to those of patient 1. The abnormal signal T2 hypointensity worsened over time, indicating progressive iron deposition in deep brain nuclei (figure 2).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for psychiatric symptoms and progressive cognitive decline includes several prototypical IEMs, such as Niemann-Pick disease type C, ALD, AIP, Wilson's disease, MLD, GM2-gangliosidosis, α- and β-mannosidosis, creatine

Figure 2 Axial FLAIR images (T=1.5) for patient 2 at age 24 (A) and age 28 (B) across the globus pallidus. Increasingly lower signal intensity from deep brain nuclei over the 4-year period is indicative of progressive brain iron accumulation.

transporter deficiency, homocystinuria, succinic semialdehyde dehydrogenase deficiency and MPS IIIB.³ However, none of these disorders have been previously associated with the MRI findings observed in these patients. The differential diagnosis appropriate for these findings later in the disease course would therefore be NBIA. Strategies to classify NBIA based on the distribution of abnormal iron signal in different brain regions has been suggested.^{5 6} The widespread pattern of involvement observed in our patients is most reminiscent of aceruloplasminemia (ACP).

ACP is a rare autosomal recessive disorder caused by mutations in the *CP* gene, which encodes ceruloplasmin.⁷ CP, a protein synthesised in the liver, has ferroxidase activity and plays a critical role in copper and iron regulation. A transcript variant of CP is expressed on the surface of astrocytes and is involved in brain iron homeostasis.⁸ CP deficiency in ACP results in iron accumulation within the brain and visceral organs. T2-weighted MRI scans of patients with ACP reveal signal hypointensities within the globus pallidus, caudate, putamen, thalamus, red nucleus and dentate.⁶ In addition to these MRI findings, the characteristic features of ACP include retinal degeneration, diabetes mellitus, and neurologic symptoms such as ataxia and involuntary movements. Psychiatric symptoms including depression and dementia have also been reported.⁹ Our patients demonstrated several features suggestive of ACP including characteristic MRI findings and a low 24-h urinary copper excretion. However, they did not exhibit retinal degeneration or diabetes mellitus, and their serum CP levels were found to be within normal limits.

OUTCOME AND FOLLOW-UP

We pursued whole exome sequencing of the nuclear family. No deleterious changes were detected in the *CP* gene, further eliminating ACP as a possible diagnosis. However, mutations were detected in *NAGLU*, which encodes the lysosomal enzyme, N-acetyl- α -D-glucosaminidase. Each parent was heterozygous for different mutations; the father had a c.1946G>T (p.W649L) change and the mother had a c.1949G>A (p.G650E) change. Both patients were compound heterozygous for the mutations (figure 3). Deficiency of *NAGLU* is diagnostic of MPS IIIB (OMIM# 252920). MPS IIIB is an autosomal recessive lysosomal storage disorder resulting in improper breakdown and storage of heparan sulfate.¹⁰ The p.G650E mutation has been previously reported in association with MPS IIIB.¹¹ The p.W649L mutation has not been described; however, another missense mutation at the same amino acid position (p.W649C) has been reported in association with the disease.¹² Urine mucopolysaccharide analysis indicated a marked excess of heparan sulfate, a pattern consistent with MPS IIIB. The diagnosis was further confirmed by an enzyme activity assay in leukocytes which revealed *NAGLU* deficiency in both patients.

DISCUSSION

MPS IIIB, also known as Sanfilippo syndrome B, is characterised by progressive mental deterioration, mild physical defects, and behavioural disturbances. The clinical course of this disease can be divided into three phases. In the first phase, which occurs between 1 and 4 years of age after a symptom-free interval, mental development begins to slow. During the second phase, which occurs around 3–4 years of age, severe behavioural problems and intellectual decline become apparent. In the third phase, behavioural issues become less pronounced, but motor function progressively declines, resulting in loss of locomotion, dysphagia and pyramidal tract lesions. Death typically occurs at

Figure 3 Whole exome short-read alignments to a reference genome (left) and Sanger validations (right) of exon 6 of *NAGLU* for the nuclear family. The mother was heterozygous for a c.1949G>A (p.G650E) mutation (highlighted in green). The father was heterozygous for a c.1946G>T (p.W649L) mutation (highlighted in red). Both affected children were compound heterozygous for the mutations.

the end of the second decade or the beginning of the third decade of life.¹³

MPS IIIB has two forms, classical and attenuated, which vary in severity and rate of progression. Individuals with the classical form have an onset of symptoms between 1 and 3 years of age, and typically die within the first two decades of life. The attenuated form, however, has a more gradual progression of symptoms. The initial clinical features are not observed until 4 years of age, and loss of expressive speech and motor function does not occur until a median age of 35 and 42.5 years, respectively.¹³ Individuals with attenuated MPS IIIB have a more gradual slowing of intellectual ability, longer preservation of motor function, and a longer life expectancy.

For the first time, we report on the accumulation of brain iron later in the disease course of MPS IIIB. MRI scans of both patients revealed a very distinct pattern of progressive decrease in T2 signal intensity in multiple deep brain nuclei in conjunction with their rapid cognitive decline. A decreased T2 signal from the deep brain nuclei, particularly in the presence of T2* GRE 'blooming', is typical of NBIA.¹⁴ The NBIA group of diseases includes pantothenate kinase-associated neurodegeneration, ACP, PLA2G6-associated neurodegeneration (PLAN), mitochondrial membrane protein-associated neurodegeneration, FA2H-associated neurodegeneration, Kufor-Rakeb syndrome, neuroferritinopathy, Woodhouse-Sakati syndrome and Friedreich's ataxia.¹⁴ The exact mechanism by which iron accumulates is unclear, but this accumulation may hold a clue to some aspects of MPS IIIB. Previous studies in murine models of MPS IIIB have suggested the possible involvement of reactive oxygen species (ROS) in neurodegeneration.¹⁵ Iron is a known

pro-oxidant and catalyses the formation of ROS; therefore, increased brain iron may contribute to the neurodegenerative events in MPS IIIB through increased ROS formation and oxidative stress. Iron deposition is also suspected of playing a role in the neurodegenerative events of Parkinson's disease, a prototypical disease of the basal ganglia which has been recently associated with *NAGLU* polymorphisms.¹⁶ However, it remains to be determined if the brain iron accumulation findings reported here could be replicated in other cases. A previous MRI study of MPS IIIB using older MRI instrumentation suggested a similar pattern of T2 signal hypointensity within the thalamus and basal ganglia in one patient, but the link between signal hypointensity and brain iron accumulation was not discussed.¹⁷ If these MRI changes are shared by other patients with MPS IIIB, it would suggest the inclusion of this disease in the differential diagnosis for NBIA. Consequently, it may be worth considering MPS IIIB in cohorts of patients with NBIA in whom a molecular diagnosis has not yet been achieved, particularly when the MRI features are reminiscent of ACP.

Aside from the previously unreported observation of brain iron accumulation, both patients in this study exhibited a disease course consistent with attenuated MPS IIIB. They experienced a very gradual decline in cognitive ability and longer preservation of speech and motor function. The early stages of their disease were dominated by behavioural and psychiatric symptoms, resulting in myriad primary psychiatric diagnoses. Since rapid cognitive decline did not occur until early adulthood, the biochemical basis of their psychiatric symptoms was not determined until significantly late in the disease course. Therefore, it is important to emphasise that MPS IIIB, as well as other IEMs, have psychiatric manifestations similar to those observed in ADD, ODD, PDD and other primary psychiatric disorders. Any signs suggesting neurodegenerative changes should prompt consideration of an IEM as the potential cause of the psychiatric presentation. Other early warning signs of an IEM would include dysmorphic features, an abnormal urine profile, a distinctly abnormal neurological examination, a family history of an IEM, or a similarly affected relative. Later in the disease course, signs would include unaccounted decline in cognitive function, language regression, or neurological deficits such as coordination difficulties, tremor, seizures, spasticity, visual symptoms and encephalopathy.

Early diagnosis of these disorders is becoming increasingly important as new disease-modifying therapeutic strategies, such as enzyme replacement or gene therapy, become a possibility for several IEMs. The efficacy of these therapies is contingent on the disease burden at the time of diagnosis and therapy initiation. Although no treatment is currently available for patients with MPS IIIB, gene therapy studies in a murine model of MPS IIIB have shown promising results. Mice who received intracranial injections of an adeno-associated viral vector containing *NAGLU* cDNA demonstrated sustained *NAGLU* expression in several brain structures, increased lifespan and improved motor function.^{18–19} Therefore, central nervous system-directed gene therapy could prove to be an efficacious treatment for patients with MPS IIIB.

In summary, MPS IIIB should be strongly considered in the differential diagnosis of patients with an early behavioural and psychiatric phenotype followed by progressive unexplained cognitive decline; this will help to significantly reduce the diagnostic odyssey of patients with MPS IIIB. Awareness and early identification of this disease will directly enhance patient management, family counselling and the success of future disease-modifying therapies.

Learning points

- ▶ In early childhood, mucopolysaccharidosis type IIIB (MPS IIIB) can manifest primarily as behavioural and psychiatric symptoms similar to those observed for attention deficit disorder and other primary psychiatric diagnoses.
- ▶ Inborn errors of metabolism should be strongly considered for patients with an early behavioural or psychiatric presentation, particularly when symptoms are accompanied by progressive cognitive and/or motor impairment.
- ▶ In our patients, MRI findings from later in the disease course of MPS IIIB indicated a pattern of progressive brain iron accumulation similar to that observed for disorders of neurodegeneration with brain iron accumulation.

Acknowledgements We would like to thank Dr Cynthia Tift and Dr Cornelius Boerkoel who independently reviewed and edited this manuscript. We would also like to thank Rena Godfrey for her contributions to reviewing this manuscript as well as her involvement in patient care during their time at the National Institutes of Health. We would like to acknowledge Dr Mary Kerber for referring this case to the Undiagnosed Diseases Program. Lastly, we would like to thank the patients' family for their cooperation and dedication.

Contributors All authors qualify for authorship based on their substantial contributions to the design, drafting, critical revision, and final approval of this manuscript. Furthermore, DL and CT contributed to the patient evaluation and interpretation of test results. JB and AT also contributed to data acquisition and analysis.

Funding The Intramural Research Program of the National Human Genome Research Institute.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Costello EJ, Mustillo S, Erkanli A, *et al.* Prevalence and development of psychiatric disorders in childhood and adolescence. *Arch Gen Psychiatry* 2003;60:837–44.
- 2 Wichstrom L, Berg-Nielsen TS, Angold A, *et al.* Prevalence of psychiatric disorders in preschoolers. *J Child Psychol Psychiatry* 2012;53:695–705.
- 3 Sedel F, Baumann N, Turpin JC, *et al.* Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. *J Inher Metab Dis* 2007;30:631–41.
- 4 Staretz-Chacham O, Choi JH, Wakabayashi K, *et al.* Psychiatric and behavioural manifestations of lysosomal storage disorders. *Am J Med Genet B Neuropsychiatr Genet* 2010;153B:1253–65.
- 5 McNeill A, Birchall D, Hayflick SJ, *et al.* T2* and FSE MRI distinguishes four subtypes of neurodegeneration with brain iron accumulation. *Neurology* 2008;70:1614–19.
- 6 Kruer MC, Boddaert N, Schneider SA, *et al.* Neuroimaging features of neurodegeneration with brain iron accumulation. *Am J Neuroradiol* 2012;33:407–14.
- 7 Harris ZL, Takahashi Y, Miyajima H, *et al.* Aceruloplasminemia: molecular characterization of this disorder of iron metabolism. *Proc Natl Acad Sci USA* 1995;92:2539–43.
- 8 Patel BN, Dunn RJ, David S. Alternative RNA splicing generates a glycosylphosphatidylinositol-anchored form of ceruloplasmin in mammalian brain. *J Biol Chem* 2000;275:4305–10.
- 9 Miyajima H, Takahashi Y, Kono S. Aceruloplasminemia, an inherited disorder of iron metabolism. *Biometals* 2003;16:205–13.
- 10 Coutinho M, Lacerda L, Alves S. Glycosaminoglycan storage disorders: a review. *Biochem Res Int* 2012;2012:471325.
- 11 Weber B, Guo XH, Kleijer WJ, *et al.* Sanfilippo type B syndrome (mucopolysaccharidosis IIIB): allelic heterogeneity corresponds to the wide spectrum of clinical phenotypes. *Eur J Hum Genet* 1999;7:34–44.
- 12 Tessitore A, Villani G, Di Domenico C, *et al.* Molecular defects in the alpha-N-acetylglucosaminidase gene in Italian Sanfilippo type B patients. *Hum Genet* 2000;107:568–76.

- 13 Valstar MJ, Bruggenwirth HT, Olmer R, *et al.* Mucopolysaccharidosis type IIIB may predominantly present with an attenuated clinical phenotype. *J Inherited Metab Dis* 2010;33:759–67.
- 14 Schipper HM. Neurodegeneration with brain iron accumulation- clinical syndromes and neuroimaging. *Biochim Biophys Acta* 2012;1822:350–60.
- 15 Villani GRD, Gargiulo N, Faraonio R, *et al.* Cytokines, neurotrophins, and oxidative stress in brain disease from mucopolysaccharidosis IIIB. *J Neurosci Res* 2007;85:612–22.
- 16 Winder-Rhodes SE, Garcia-Reitbock P, Ban M, *et al.* Genetic and pathological links between Parkinson's Disease and the lysosomal disorder Sanfilippo Syndrome. *Mov Disord* 2012;27:312–15.
- 17 Zafeiriou DI, Savvopoulou-Augoustidou PA, Sewell A, *et al.* Serial magnetic resonance imaging findings in mucopolysaccharidosis IIIB (Sanfilippo's syndrome B). *Brain Dev* 2001;23:385–89.
- 18 Fu H, Samulski RJ, McCown TJ, *et al.* Neurological correction of lysosomal storage in a mucopolysaccharidosis IIIB mouse model by adeno-associated virus-mediated gene delivery. *Mol Ther* 2002;5:42–9.
- 19 Heldermon CD, Ohlemiller KK, Herzog ED, *et al.* Therapeutic efficacy of bone marrow transplant, intracranial AAV-mediated gene therapy, or both in the mouse model of MPS IIIB. *Mol Ther* 2010;18:873–80.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit

<http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow