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Case Report

Mucopolysaccharidosis Type III (Subtype IIIB) Diagnosis as a Spectrum Disorder: a Case Report from Kosovo

Lidvana Spahiu[1], Emir Behluli[1], Rifat Hadziselimovic[2], Thomas Liehr[3], Gazmend Temaj[4]

[1] Department of Pediatrics, Medical Faculty, University of Pristina, Pristina, Kosovo
[2] Faculty of Science, University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[3] Friedrich Schiller University, Institute for Human Genetics, Jena, Germany
[4] Department of Human Genetics, Faculty of Medicine and Pharmacy, College UBT, Pristina, Kosovo

Corresponding author: Gazmend Temaj, Department of Human Genetics, Faculty of Medicine and Pharmacy, College UBT, Kalabria nn, Pristina, Kosovo; Email: gazmend.temaj@ubt-uni.net; Tel.: 0038345803450

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Abstract

Mucopolysaccharidosis type IIIB (MPS IIIB), also known as Sanfilippo syndrome type B, is a metabolic disease caused by mutations in both alleles of the NAGLU gene encoding for the enzyme α-N-acetylglucosaminidase. A malfunction of this enzyme causes inability to degrade heparan sulfate, which leads to accumulation of glycosaminoglycans in the cells. MPS IIIB is associated with different symptoms such as neurodegeneration, extreme hyperactivity, sleeping problems, aggressive behavior, reduced fear, and cognitive deterioration. The condition is by now not curable. Here we describe a patient with MPS IIIB diagnosed at the age of 5 presenting with communication problems, motor dysfunctions, and speech and sleeping problems.

Standard biochemical tests for neurodegenerative disorders and DNA analyses including NAGLU mutation screening were performed. We also did some psychological tests assessing the patient's communication skills and behavior.

The patient was heterozygote for two mutations in the gene NAGLU (Y140C and Ser169fs). Thus, he suffered from MPS IIIB due to two mutations in the disease-causing gene.

The patient presented with clear signs and symptoms of MPS IIIB with at least one of the two mutations affecting the α-N-acetylglucosaminidase protein function severely. Here we report the combination of a well-known and previously unreported mutation in the NAGLU gene; this could be dependent on geographical origin of the patient, which needs to be clarified by molecular studies of more MPS IIIB patients from Southeast Europe.

Keywords

clinical analysis, MPS IIIB, NAGLU gene

INTRODUCTION

Mucopolysaccharidosis is a rare genetic disease caused by the deficiency of an enzyme that catalyzes the metabolism of glycosaminoglycans (GAG) in lysosomes. GAG accumulation has been shown to cause dysfunction on cellular, tissue, and organ levels leading to multiple systemic effects, with phenotypic consequences such as abnormal facial features.[1] Mucopolysaccharidosis type III (MPS III, or Sanfilippo syndrome) consists of four subtypes, MPS IIIA, MPS IIIB, MPS IIID, and MPS IIIE, in which heparan sulfate (HS) is accumulated.[2] MPS III patients are typically affected by hyperactivity, sleeping problems, and progressive mental and cognitive deterioration. The majority of MPS III patients cannot speak, and even if they develop speech to some extent, it is gradually lost during the course of the disease. The average life expectancy of these patients is two decades.[2,3]

Patients with MPS III show normal development after birth; later, in the first phase, they have recurrent ear, nose, throat, and gastrointestinal problems. In the second phase, their behavior changes including afore mentioned hyperactivity and sleeping disorders. In the third and last phase, the child experiences loss of intellectual capabilities and motor functions.[4] Overall, patients with MPS (specifically with MPS IIIB) present with neurocognitive signs and symptoms.[5] The age at diagnosis for MPS IIIB patients can be very different, from 4 years to adulthood; children under suspicion of MPS IIIB suffer from idiopathic symptoms, developmental delay, and attention-deficit/hyperactivity disorders.[5]

The gene *NAGLU* located in chromosome 17q21 is responsible for the production of normal lysosomal enzyme called α-N-acetylglucosaminidase. The inheritance of MPS IIIB is autosomal recessive; accordingly, either parents may be carrier of one copy of a mutated gene, but they do not show any symptoms or signs of the disease, and/or one of the parent's gametes provides a new mutation in NAGLU.[6,7] Yet, there is no cure for MPS IIIB; still, quick and proper diagnosis can help families to get adequate support by the health system.[8] As MPS IIIB patients can show variable clinical expression detailed genotype-phenotype correlations are necessary. Alpha-N-acetylglucosamidase is assessed by fluorimetry, and the values for alpha-N-acetylglucosamidase in our patients were <0.3 (LOQ) μmol/L/h (normal value ≥1.5 μmol/L/h). Here we describe a new MPS IIIB patient characterized clinically and on molecular genetic level.

CASE REPORT

Clinical analysis

*The male patient had a birth weight of 3250 g and a head circumference of 34 cm. He started to hold his head and follow by observing objects at the age of 5 months. At 5 years of age, the patient weighed 32 kg, and his head circumference was 46 cm. There was no family history of mental retardation or neurological disorders. On physical examination, facial dysmorphisms including prominent eyebrows, low set ears, and low hairline were diagnosed, together with stiffness of extremities, and enlarged liver (according to the ultrasound: crania-caudal length 17 cm). During the interview with parents, they said that their child could not control urination, which was also associated with constipation. The patient showed motor development retardation, such as inability to walk, and mental retardation **(Table 1)**.*

Table 1. Clinical features of the disease manifested in our patient. (Adapted from Zhou J, Lin J, Leung WT, Wang L. A basic understanding of mucopolysaccharidosis: Incidence, clinical features, diagnosis, and management. Intractable Rare Dis Res 2020; 9(1):1–9. doi: 10.5582/irdr.2020.01011.[15])

Clinical features	MPS III	Our patient
Coarse facial features	-/+	+
Cognitive retardation	+	+
Epilepsy	+	+
Hepatosplenomegaly	+	+
Valve disease	+	-
Inguinal and umbilical hernias	+	+
Corneal clouding	+	-
Kyphoscoliosis	+	+
Hearing loss	+	+
Teeth abnormalities	+	+
Enlarged tongue	+	-

*In magnetic resonance imaging (MRI), the head showed a periventricular leukomalacia with diffuse occipital periventricular lesions and partially in white substance of cerebellum with hypotrophy of the dorsal part of corpus callosum and bilateral cortical hypotrophy of cerebellum in frontal gyros and less in parietal-occipital **(Fig. 1)**.*

Biochemical analysis

*Biochemical analysis was performed and results are summarized in **Table 2**. Alanine aminotransferase (ALT) and*

Table 2. Results of biochemical analysis of blood and urine for our case patient and normal values (abnormal values shown in bold)

Type of analysis	Biochemical analysis	
	This patient	Reference ranges
ALT	86 U/l	42 U/l
AST	47 U/l	42 U/l
Cholesterol	3.4 mmol/l	<6.5 mmol/l
HDL cholesterol	1.07 mmol/l	1.68 mmol/l
LDL cholesterol	3.01 mmol/l	3.9–4.9 mmol/l
Triglycerides	0.92 mmol/l	1.4–1.8 mmol/l
Glycaemia	4.3 mmol/l	4.0–5.9 mmol/l
BUN	3.7 mg/dl	10–20 mg/dl
Creatinine	62.0 μmol/l	44–88 μmol/l
Platelets	**87×10^9/l**	150–400×10^9/l
α-N-acetylglucosamine	**<0.3 μmol/l/h**	<1.5 μmol/l/h

ALT: alanine aminotransferase; AST: aspartate transaminase; HDL: high density lipoprotein; LDL: low density lipoprotein; BUN: blood urea nitrogen

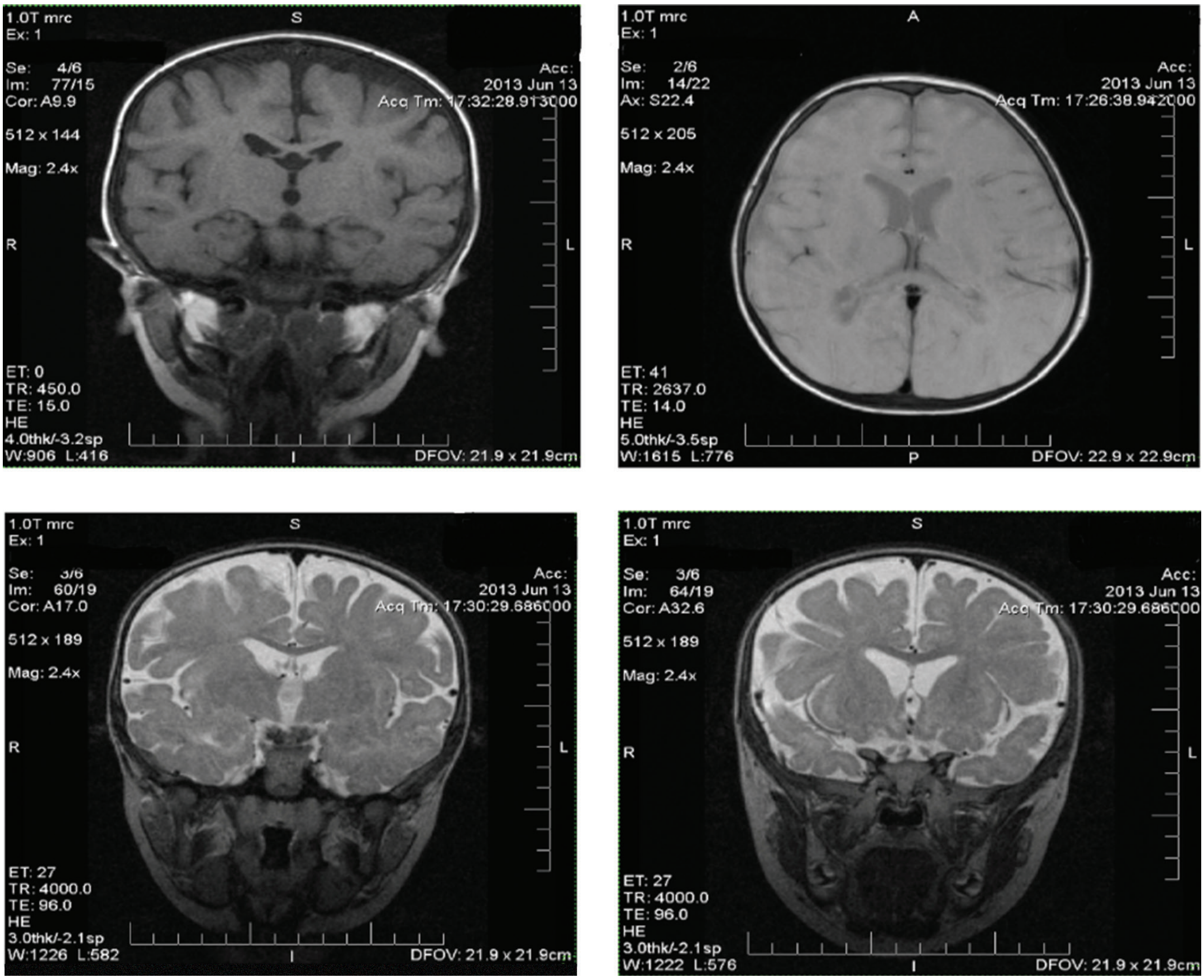

Figure 1. MRI of patient X. Periventricular leukomalacia is the description for mucopolysaccharidosis.

aspartate transaminase (AST) were elevated; the high- and low-density lipoproteins and triglycerides were decreased; the blood urea nitrogen and the platelets were decreased. Also, the α-N-acetylglucosamine was decreased by 5 times.

An array comparative genomic hybridization analysis was performed which indicated no pathogenic copy number variations. Sanger sequencing of the NAGLU gene identified a missense mutation (the amino acid Tyr was replaced with Cys (Y140C)) and a frameshift deletion in position (Ser169fs) in the patient ***(Table 3).***

Table 3. Genotype and national origin of MPS IIIB patients compared with our patient

Patients	Allele 1	Allele 2	Origin
1	Y140C	Ser169fs	KS (Kosovo - present case)
2	219-237del19	Y140C	UK (United Kingdom)
3	Y140C	R626X	GR (Greece)
4	Y140C	L497V	NL (Netherland)

DISCUSSION

The present patient is a typical MPS IIIB case **(Table 1)**, which is supported by the biochemical data **(Table 2)**. The targeted genetic analysis for mutations in the *NAGLU* gene confirmed the clinical suspicions and established the definitive diagnosis for this patient. As the gene product of *NAGLU* has 743 amino acids, a frameshift causing deletion in position 169 and a change from tyrosine to cysteine in position 140 must lead to severe impairment of α-N-acetylglucosaminidase. Unfortunately, the patient's parents declined to have their own DNA sequenced. Thus, the origin of the Y140C (maternal or paternal) and of the Ser169fs mutation (parental or de novo) could not be clarified.

While the Y140C mutation in the *NAGLU* gene has already been reported by other researchers[9-14], the Ser169fs mutation has, to the best of our knowledge, not been reported yet **(Table 2)**. Also, the Y140C mutation is among the three mutations accounting for approximately 36% of all *NAGLU* gene mutations in connection with MPS IIIB.[10]

In conclusion, the detailed characterization of the underlying genetic cause for the herein reported MPS IIIB patient was important for the index and his family: (i) the patient received well-founded diagnosis and prognosis, (ii) parents were guided to and informed about corresponding family support groups, and (iii) in case the parents wish to have further children, they will be able to check the unborn child for its mutation status concerning the *NAGLU* gene. Besides, the yet unreported *NAGLU* gene mutation (Ser169fs) being identified here for the first time requires future studies to clarify if it is more frequent in Balkan region.

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Statement of ethics

Samples from the patients were obtained in accordance with the principles of the Declaration of Helsinki. Written informed consent for genetic testing was obtained from patient and/or their parent/guardian.

Competing Interests

The authors have declared that no competing interests exist.

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Диагноз мукополисахаридоза типа III (подтип IIIB) как расстройство спектра: клинический случай из Косово

Лидвана Спахиу[1], Емир Бехлули[1], Рифат Хаджиселимович[2], Томас Лийр[3], Газменд Темадж[4]

[1] Кафедра педиатрии, Медицинский факультет, Университет Приштины, Приштина, Косово

[2] Факультет природных наук, Университет Сараево, Сараево, Босния и Герцеговина

[3] Университет имени Фридриха Шиллера, Институт генетики человека, Йена, Германия

[4] Кафедра генетики человека, Факультет медицины и фармации, Университет бизнеса и технологий, Приштина, Косово

Адрес для корреспонденции: Газменд Темадж, Кафедра генетики человека, Факультет медицины и фармации, Университет бизнеса и технологий, Приштина, Косово; Email: gazmend.temaj@ubt-uni.net; тел.: 0038345803450

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Резюме

Мукополисахаридоз типа IIIB (MPS IIIB), также известный как синдром Санфилиппо типа B, представляет собой метаболическое заболевание, вызванное мутациями в обоих аллелях гена NAGLU, кодирующего фермент α-N-ацетилглюкозаминидазу. Нарушение работы этого фермента приводит к неспособности расщеплять гепарансульфат, что приводит к накоплению в клетках гликозаминогликанов. MPS IIIB связан с различными симптомами, такими как нейродегенерация, крайняя гиперактивность, проблемы со сном, агрессивное поведение, уменьшение страха и ухудшение когнитивных функций. Состояние пока неизлечимо. Здесь мы описываем пациента с MPS IIIB, диагностированного в возрасте 5 лет, у которого были проблемы с общением, моторные дисфункции, а также проблемы с речью и сном.

Были проведены стандартные биохимические тесты на нейродегенеративные заболевания и анализы ДНК, включая скрининг мутаций NAGLU. Мы также провели несколько психологических тестов, оценивающих коммуникативные навыки и поведение пациента.

Пациент был гетерозиготным по двум мутациям в гене NAGLU (Y140C и Ser169fs). Таким образом, он страдал от MPS IIIB из-за двух мутаций в гене, вызывающем болезнь.

У пациента были чёткие признаки и симптомы MPS IIIB с по крайней мере одной из двух мутаций, серьёзно влияющих на функцию белка α-N-ацетилглюкозаминидазы. Здесь мы сообщаем о комбинации хорошо известной и ранее неизвестной мутации в гене NAGLU; это может зависеть от географического происхождения пациента, что необходимо уточнить с помощью молекулярных исследований большего количества пациентов с MPS IIIB из Юго-Восточной Европы.

Ключевые слова

клинический анализ, ген MPS IIIB, ген NAGLU