





A retrospective study on neuropsychiatric presentations of mucopolysaccharidoses

Nöropsikiyatrik semptomlarla başvuran mukopolisakkaridoz olguları

Fehime Erdem  Havva Yazıcı  Merve Yoldaş Çelik  Ayşe Yüksel Yanbolu 
Ebru Canda  Sema Kalkan Uçar  Mahmut Çoker 

Ege University Faculty of Medicine, Department of Pediatrics, Division of Pediatrics Metabolism and Nutrition, İzmir, Türkiye

ABSTRACT

Aim: Mucopolysaccharidoses (MPS) are a heterogeneous group of diseases characterised by systemic manifestations due to impaired glucosaminoglycans (GAG) degradation within lysosomes. Mucopolysaccharidosis type II (MPS II, Hunter) is a lysosomal disease caused by mutations in the iduronate-sulfatase (IDS) gene. MPS II is inherited in an X-linked recessive manner. Mucopolysaccharidosis type III (MPS III, Sanfilippo) is an autosomal recessive lysosomal disease. It has four subtypes (A, B, C, and D). MPS II and III particularly exhibit significant central nervous system involvement. Early clinical manifestations may include cognitive delay, behavioural disturbances, progressive behaviour-sleep problems, delayed speech, autism-like features, and unexplained intellectual disability.

Materials and Methods: In this retrospective study, we recorded the clinical findings of patients who were diagnosed with mucopolysaccharidosis type II and III and presented with neuropsychiatric symptoms such as seizures, developmental delay, speech impairment, and loss of neurological milestones.

Results: The study included eleven cases, comprising 6 (54.5%) males and 5 (45.5%) females. Among them, 4 (50%) were diagnosed with MPS IIIA, 3 (37.5%) with MPS IIIB, and 1 (12.5%) with MPS IIIC. Six patients (54.5%) had speech delay, while two (18.1%) had cognitive delay, and three (27.2%) had hyperactivity, with nine (81.8%) experiencing motor delay. The mean age at presentation was 8.4 (± 5.2 SD) years, with six patients (54.5%) receiving physical therapy and special training.

Conclusion: In patients presenting with neuropsychiatric symptoms, consideration of mucopolysaccharidoses along with urine GAG, enzymatic assays and, when indicated, genetic testing is crucial for early diagnosis and intervention.

Keywords: Cognitive impairment, hyperactivity, mucopolysaccharidoses, speech impairment,

ÖZ

Amaç: Mukopolisakkaridozlar (MPS); glukozaminoglikanların (GAG) lizozom içerisinde yıkılmaması sonucu çoklu sistem tutulumlarına neden olan heterojen bir hastalık grubudur. MPS II ve III' de santral sinir sistemi tutulumu daha ön plandadır. Erken dönemde bilişsel gerilik, davranış problemleri, ilerleyici davranış-uyku problemleri, gecikmiş konuşma, otizm benzeri bulgular, sebebi bilinmeyen zihinsel yetersizlik görülebilir.

Corresponding author: Fehime Erdem

Ege University Faculty of Medicine, Department of Pediatrics, Division of Pediatrics Metabolism and Nutrition, İzmir, Türkiye

E-mail: fehimeerdem@gmail.com

Application date: 30.08.2024

Accepted: 21.04.2025

Gereç ve Yöntem: Mukopolisakkaridoz II ve III tanısı ile izlenen nöbet, gelişim basamaklarında gerilik, konuşma gecikmesi, nörolojik gelişim basamaklarında kayıp gibi nöropsikiyatrik semptomlarla başvuran hastaların sonuçları retrospektif olarak kaydedildi.

Bulgular: Çalışmaya 11 olgu dahil edildi. 6 (%54,5)'sı erkek, 5 (%45,5)'i kadındı. MPS III olgularının 4 (%50)'ü MPS 3A, 3 (%37,5)'ü MPS IIIB, 1 (%12,5)'i MPS IIIC tanılıdır. Başvuruda 6 (%54,5)'sinde konuşma geriliği, 2 (%18,1)'i bilişsel gerilik, 3 (%27,2)'sinin ise hiperaktivite varken ek olarak 9 (%81,8)'inde motor gerilik de eşlik etmekteydi. Başvuru yaş ortalamaları 8,4 ($\pm 5,2$ SDS) yıldı. 6 (%54,5)'sı fizik tedavi rehabilitasyon ve özel eğitim desteği almaktaydı.

Sonuç: Nöropsikiyatrik semptomlarla başvuran hastalarda mukopolisakkaridozların da düşünülerek, İdrar GAG, enzimatik ve gereğinde genetik analizlerin yapılması, erken teşhis ve tedavi açısından önemlidir.

Anahtar Sözcükler: Mukopolisakkaridoz, Hiperaktivite, Konuşma geriliği, Bilişsel gerilik

INTRODUCTION

Mucopolysaccharidoses (MPS) are rare inherited lysosomal diseases of extensive clinical heterogeneity, with ongoing development of new treatments. Due to the inability to degrade existing glycosaminoglycans (GAG) within the lysosome, accumulations lead to systemic involvement and clinical manifestations (1, 2). The diagnosis is based on cellular enzyme level measurement, urinary GAG excretion, and genetic analysis. Types MPS I, II, IIIA, IIIB, IIIC, IIID and VII primarily involve the central nervous system (1). Changes in the central nervous system include atrophic alterations and abnormalities in white matter and perivascular spaces, hydrocephalus, increased intracranial pressure, and compressive myelopathy (3). Seizures may also occur due to central nervous system involvement.

In this study, we evaluated clinical records of our patients with MPS II and III, who primarily presented with central nervous system involvement.

Mucopolysaccharidosis type II (MPS II, Hunter syndrome) is a lysosomal storage disease caused by hemizygous pathogenic variants in the *IDS* gene. The deficient enzyme is iduronate sulfatase (IDS). Unlike other mucopolysaccharidoses, which are inherited in an autosomal recessive manner, MPS II is inherited in an X-linked recessive manner. The accumulation of heparan sulphate and dermatan sulphate leads to clinical manifestations. It is characterized by coarse facial features, visceromegaly, bone-joint deformities, hernias, upper airway stenosis and progressive neurological involvement. The prevalence is 1 in 100.000 (2). Neurological symptoms become progressively more prominent by the age of 4 years. Enzyme replacement therapy can address

the systemic aspects of the disease, while it does not affect the central nervous system. Therefore, behavioral therapy and special education are of great importance (1).

Mucopolysaccharidosis type III (MPS III, Sanfilippo) is an autosomal recessive lysosomal disease (3) with a frequency of 1.5-1.9 per 100.000 births. It has four subtypes (A, B, C, and D). MPS IIIA is associated with heparan N – sulfatase enzyme deficiency due to pathogenic variants in the *SGSH* gene (3), while MPS IIIB is due to N – acetylglucosaminidase enzyme deficiency caused by pathogenic variants in the *NAGLU* gene (4). MPS IIIC results from a deficiency in the acetyl – CoA glucosamine – N – acetyltransferase enzyme due to pathogenic variants in the *HGSNAT* gene, and MPS IIID is linked to a deficiency in the N-acetyl glucosamine 6-sulphatase enzyme due to pathogenic variants in the *GNS* gene. The accumulation of heparan sulphate leads to symptoms, starting with cognitive and behavioural changes in the initial 10 years of life, followed by eating problems and loss of fine and gross motor skills (3). While early neurological development is typical, cognitive changes begin after infancy, with behavioural changes and autism-like manifestations appearing over time. As heparan sulfate accumulates and persists and the disease progresses, central system involvement increases, leading to a shortened life span (5, 6).

The presented study aims to highlight that somatic complaints or physical examination findings may sometimes be subtle in the early stages in patients presenting with cognitive impairment, behavioural problems, progressive behavioural and sleep problems, delayed speech, autism-like symptoms,

intellectual disability of unknown cause and epilepsy with motor loss. Investigating and considering other systemic findings in patients presenting with these symptoms is crucial. The diagnosis of MPS with severe central nervous system involvement, such as MPS II and III, should be considered as part of the differential diagnosis.

MATERIALS and METHODS

We retrospectively reviewed the medical records of patients who were diagnosed with mucopolysaccharidosis in the Department of Pediatric Metabolism and Nutrition, Ege University Faculty of Medicine. The study included patients presenting with neuropsychiatric symptoms such as seizures, developmental delay, speech delay, and loss of neurological development milestones. Data on patients with comorbidities or those presenting with different symptoms were excluded.

Data were collected from patient medical records about their diagnosis, gender, family history of consanguinity, age at presentation, presenting symptoms, current age, history of seizures, gait status and neuromotor evaluation at presentation, and physical examination findings at presentation (growth evaluation, rough facial features, organomegaly). Additionally, cranial imaging results for hydrocephalus, X-ray results for bone joint involvement, ECHO (echocardiography) reports for cardiac involvement, hearing evaluation results, urine glycosaminoglycan measurement, enzymatic and genetic analysis results and information on whether the patient received special training, physical therapy and rehabilitation were also obtained. Data analysis was performed with the statistical package SPSS Inc., version 21.0 (Chicago, IL, USA). Continuous variables are displayed as arithmetical means plus or minus SD; categorical variables are shown as frequencies or percentages.

RESULTS

Data from eleven patients were analysed. Six (54.5%) patients were male, and five (45.5%) were female. There was no consanguinity between the parents in six (54.5%) patients, while three (27.7%) patients had consanguineous parents. There was no consanguinity in the two patients, but the parents were from the same village. Patients 3-4 and 5-6 were siblings. Three (27.7%)

patients with MPS II received regular enzyme replacement therapy. Eight (72.7%) patients were diagnosed with MPS III. Among the MPS III cases, four (50%) were diagnosed with MPS IIIA, three (37.5%) with MPS IIIB, and one (12.5%) with MPS IIIC. The mean age at presentation was 8.4 ± 5.2 years. The current mean age of the patients was 12.9 ± 6.5 years (Table-1).

Of all patients, nine (81.9%) had a history of term birth, and two (18.1%) were born prematurely. Those born at term had normal body weight for their gestational age, while the premature infants had low birth weight for their gestational age.

An analysis of the presenting symptoms showed that six (54.5%) patients had a speech delay, two (18.1%) had a cognitive delay, and three (27.2%) had hyperactivity. The ninth patient, who initially presented with a speech delay, experienced a loss of motor skills and gait over the past 2.5 years and a speech delay over the past year (Table-1).

Two (18.1%) patients had a history of seizures before presenting to our department. EEG (electroencephalography) analysis revealed multifocal epileptiform abnormalities. At presentation, three patients (27.7%) were unable to walk (the ninth patient had lost it in the past 2.5 years), four (36.3%) could walk with support, and 4 (36.3%) could walk unassisted. Of the patients whose neuromotor development was evaluated at presentation, two (18.1%) had motor skills consistent with their peers, eight (72.7%) were behind their peers, and one (9.09%) had initially developed motor skills on par with their peers but later regressed and was behind at the time of examination (Table-1).

Physical examination of the patients showed that their growth was comparable to that of their peers, and none of them had signs of malnutrition. The mean body weight SDS was $0.89 (\pm 1 \text{ SD})$, the mean height SDS was $0.93 (\pm 1.29 \text{ SD})$, and the mean head circumference SDS was $0.98 (\pm 0.74 \text{ SD})$. Six patients (54.5%) had coarse facial appearance, three (27.2%) had hepatomegaly, and one (9.09%) had adenoid hyperplasia. Two patients (18.1%) had a range of motion limitations, and both were diagnosed with MPS II. None of the patients had hernia or Mongolian spots. Of the six patients for whom cranial imaging was available, two had hydrocephalus, and one had a ventriculoperitoneal shunt. Bone and joint involvement was found in four (40%) of the 10 patients with available bone radiographs. Hearing

evaluation was performed on six patients, with five (83.3%) showing hearing loss. The cardiac assessment was conducted on eight patients, with five (62.5%) exhibiting valvular involvement, primarily affecting the mitral valve. Six patients (54.5%) received special training and physical therapy rehabilitation. Two patients (18.1%) were fed by gastrostomy, while the others were able to tolerate oral nutrition (Table-2).

During the diagnostic process, urine glycosaminoglycan levels were elevated in eight

patients (72.7%) and normal in the remaining patients. Enzymatic analysis of peripheral blood showed significantly low intracellular enzymatic levels in ten patients (90.9%), while the enzymatic levels in the second patient diagnosed with MPS IIIA were within normal limits. Additionally, the diagnosis of seven patients (63.6%) was confirmed through genetic testing (Table-3).

Table-1. Neurological findings at presentation

Patient	Diagnosis	Gender	Age at presentation/ Current age (years)	Follow-up (month)	Symptoms	At presentation		
						Seizure	Gait status	Neuromotor impairment
1	MPS IIIA	M	4.3/19	14.7	Speech delay	+	None	+
2	MPS IIIA	F	5.0/9.8	4.8	Speech delay	-	Assisted	+
3	MPS IIIB	F	19.9/23.6	3.7	Cognitive delay	-	Assisted	+
4	MPS IIIB	M	15.5/19.2	3.7	Cognitive delay	-	Assisted	+
5	MPS IIIA	F	8.1/11.9	3.8	Speech delay	+	None	+
6	MPS IIIA	M	8.1/11.9	3.8	Speech delay	-	Free	+
7	MPS II	M	4.6/9 ex	4.4	Hyperactivity	-	Assisted	+
8	MPS II	M	3.6/4.8	1.2	Hyperactivity	-	Free	-
9	MPS IIIC	F	11/18.7	7.7	Speech delay	-	None	+
10	MPS IIIB	F	6.4/11 ex	4.6	Speech delay and	-	Free	-
11	MPS II	M	5.3/14.5	9.2	Hyperactivity Speech delay	-	Free	+

F: Female, M: Male

Table-2. Results suggestive of MPS at presentation

Patient	Diagnosis	Coarse face	Visseromegaly	Joint stiffness	Cardiac Findings	Behavioural + Physical Therapy	Nutrition
1	MPS IIIA	+	-	Yes	MVP	+	PEG
2	MPS IIIA	+	-	No	NA	+	Oral
3	MPS IIIB	-	-	NA	NA	-	Oral
4	MPS IIIB	-	-	No	NA	-	Oral
5	MPS IIIA	+	HM	Yes	MVP, MR	-	Oral
6	MPS IIIA	+	HM	Yes	AR	-	Oral
7	MPS II	+	HM	No	MVP,MR,AR	+	Oral
8	MPS II	-	-	No	-	+	Oral
9	MPS IIIC	-	-	No	-	-	Oral
10	MPS IIIB	+	-	No	-	+	Oral
11	MPS II	+	-	Yes	MVP, MR	+	PEG

AR: Aortic regurgitation, HM: Hepatomegaly, MR: Mitral regurgitation, MVP: Mitral valve prolapsus, NA: Not applicable, PEG: percutaneous endoscopic gastrostomy

Table-3. Specific laboratory analyses

Patient	Diagnosis	Urine GAG	Enzyme (DBS)	level	Genetic analysis	
1	MPS IIIA	H	L		<i>SGSH</i>	c.7_16del; c.7_16del
2	MPS IIIA	H	N		<i>SGSH</i>	c.496C>T; c.939_940insCAL
3	MPS IIIB	H	L		<i>NAGLU</i>	c.934G>A; c.934G>A
4	MPS IIIB	H	L		<i>NAGLU</i>	c.934G>A; c.934G>A
5	MPS IIIA	H	L		NA	
6	MPS IIIA	H	L		NA	
7	MPS II	H	L		NA	
8	MPS II	N	L		<i>IDS</i>	c.394G>A
9	MPS IIIC	N	L		<i>HGNSNAT</i>	c.518G>A; c.518G>A
10	MPS IIIB	N	L		NA	
11	MPS II	H	L		<i>IDS</i>	Complex rearrangement

DBS: Dry Blood Spot Sample, Hem: Hemizygous, Het: Heterozygous, H: High, Hom: Homozygous, L: Low, N: Normal, NA: Not applicable

DISCUSSION

Mucopolysaccharidoses are a group of inherited lysosomal storage diseases characterised by various skeletal anomalies, coarse facial features, progressive psychomotor impairment, and cardiac and pulmonary involvement due to the accumulation of glycosaminoglycans (7). MPS II and III are hereditary rare metabolic diseases where cognitive and behavioural problems are more prominent than other system involvement. Enzyme replacement therapy is available for MPS II but insufficient to prevent central nervous system manifestations. Currently, there is no specific treatment for MPS III (8). This underscores the importance of exploring new treatment options such as genistein, intrathecal enzyme therapies, and oral substrate reduction therapies (9-11).

A study evaluating 17 MPS patients aged 2-16 years with autism-like symptoms showed no significant differences between the MPS III types in terms of behavioural changes and symptom differentiation. In the questionnaires administered to families and patients, traits such as interest in limited topics, repetitive behaviours, decreased social awareness and sensitivity were similar to those observed in autism spectrum disorder. It was concluded that families' need for social assistance also increased (12).

In a study that sleep disturbance, behavioural problems, repetitive movements, continuous rocking, sleep problems, aggression, and hyperactivity observed in behavioural and attitude

questionnaires administered to families with children having mucopolysaccharidosis, similar to our findings, it was suggested that highlighting these issues could help address the challenges experienced by families and that interaction with other families dealing with similar conditions might increase motivation (13).

A study involving 12 patients diagnosed with MPS IIIA, predominantly presenting with hyperactivity and cognitive delay, highlighted that other supportive therapies, such as risperidone, might be beneficial (14).

Seizures can occur in patients due to central nervous system involvement. In patients with cognitive delay, motor delay and behavioural problems, looking for additional symptoms suggestive of MPS, such as organomegaly, coarse facial features and cardiopulmonary involvement, can provide valuable guidance. In our study, two patients referred with isolated neurological findings had seizures. One of these two patients had organomegaly. A review examining seizures in MPS patients showed similar results (15).

It is essential to consider MPS in patients presenting with neurologic symptoms, even without additional physical examination findings. Urine GAG measurement can be used as a screening test. However, as seen in our study cases with normal urine GAG measurements were reported previously (2). Genetic analysis may be helpful in suspected cases if additional enzymatic analyses and supportive findings are present.

Even without definitive treatment, early diagnosis is crucial for providing supportive therapies, monitoring disease progression and implementing additional therapies. neurotoxicity group had higher TGF- β levels. Similar to the positive control L-DOPA group, treatment with Iturin A dramatically decreased inflammation in these neurotoxic cells by lowering TGF- β levels. In addition, when all these findings are evaluated together, these cytokines/chemokines seem to work synergistically and thus contribute to neurodegeneration and neuroprotection by supporting each other.

CONCLUSION

Mucopolysaccharidoses should be considered in the differential diagnosis of individuals with behavioural problems, cognitive delay, autism-like symptoms and progressive neurological findings. Supportive findings may be identified in patients presenting with these symptoms through detailed systemic examination and system scans. Urine GAG level can be used as a screening test in these patients, while enzymatic or genetic analysis is essential for those with elevated levels.

Conflicts of interest: Authors declared no conflict of interest.

References

1. Barone R, Pellico A, Pittalà A, Gasperini S. Neurobehavioral phenotypes of neuronopathic mucopolysaccharidoses. *Italian Journal of Pediatrics*. 2018;44(2):107-15.
2. Okuyama T, Eto Y, Sakai N, Minami K, Yamamoto T, Sonoda H, et al. Iduronate-2-Sulfatase with Anti-human Transferrin Receptor Antibody for Neuropathic Mucopolysaccharidosis II: A Phase 1/2 Trial. *Mol Ther*. 2019;27(2):456-64.
3. Wijburg FA, Whitley CB, Muenzer J, Gasperini S, Del Toro M, Muschol N, et al. Intrathecal heparan-N-sulfatase in patients with Sanfilippo syndrome type A: A phase IIb randomized trial. *Mol Genet Metab*. 2019;126(2):121-30.
4. Değerliyurt A, Yayıcı Köken Ö, Teker ND, Aktaş D. Significant neuropsychiatric symptoms: three mucopolysaccharidosis type IIIB cases, two of whom were siblings with a novel NAGLU gene mutation. *Neurocase*. 2021:1-6.
5. Sampayo-Cordero M, Miguel-Huguet B, Pardo-Mateos A, Malfettone A, Perez-Garcia J, Lombart-Cussac A, et al. Agreement between results of meta-analyses from case reports and clinical studies, regarding efficacy and safety of idursulfase therapy in patients with mucopolysaccharidosis type II (MPS-II). A new tool for evidence-based medicine in rare diseases. *Orphanet J Rare Dis*. 2019;14(1):230.
6. Abreu NJ, Selvaraj B, Truxal KV, Moore-Clingenpeel M, Zumberge NA, McNally KA, et al. Longitudinal MRI brain volume changes over one year in children with mucopolysaccharidosis types IIIA and IIIB. *Molecular Genetics and Metabolism*. 2021;133(2):193-200.
7. Ergun P, Kagnıcı M, Ucar S, Coker M, Akcay Y, Sozmen E. Possible diagnostic markers for Mucopolysaccharidoses; Cathepsin-D, Galectin-3 and Chitotriosidase. *IZMIR DR BEHCET UZ COCUK HASTANESI DERGISI*. 2017;7(2).
8. Escolar M, Bradshaw J, Byers VT, Giugliani R, Golightly L, Lourenço CM, et al. Development of a Clinical Algorithm for the Early Diagnosis of Mucopolysaccharidosis III. *Journal of Inborn Errors of Metabolism and Screening*. 2020;8.
9. Ghosh A, Rust S, Langford-Smith K, Weisberg D, Canal M, Breen C, et al. High dose genistein in Sanfilippo syndrome: A randomised controlled trial. *J Inherit Metab Dis*. 2021;44(5):1248-62.
10. Seker Yilmaz B, Davison J, Jones SA, Baruteau J. Novel therapies for mucopolysaccharidosis type III. *Journal of Inherited Metabolic Disease*. 2021;44(1):129-47.
11. Yazici H, Canda E, Er E, Ucar S, Onay H, Ozkinay F, et al. Clinical, biochemical and molecular characteristics of fifteen patients with mucopolysaccharidosis type II in Western Turkey. *JOURNAL OF PEDIATRIC RESEARCH*. 2018;5(1).

12. Wolfenden C, Wittkowski A, Jones SA, Rust S, Hare DJ. Autism spectrum disorder symptomatology in children with mucopolysaccharide disease type III. *British Journal of Learning Disabilities*. 2019;47(1):5-11.
13. Hoffmann F, Hoffmann S, Kunzmann K, Ries M. Challenging behavior in mucopolysaccharidoses types I–III and day-to-day coping strategies: a cross sectional explorative study. *Orphanet journal of rare diseases*. 2020;15(1):1-14.
14. Ucar SK, Ozbaran B, Demiral N, Yuncu Z, Erermis S, Coker M. Clinical overview of children with mucopolysaccharidosis type III A and effect of Risperidone treatment on children and their mothers psychological status. *Brain and Development*. 2010;32(2):156-61.
15. Scarpa M, Lourenço CM, Amartino H. Epilepsy in mucopolysaccharidosis disorders. *Molecular genetics and metabolism*. 2017;122:55-61.