

Maroteaux-Lamy syndrome–mucopolysaccharidosis type VI: a case report (errors and complications)

**L.K. Mikhailova, A.A. Kuleshov, N.I. Arzhakova, T.V. Sokolova, M.S. Vetrile, I.V. Shvachka,
O.A. Poliakova, I.S. Gromov**

Priorov Central Scientific Research Institute of Traumatology and Orthopaedics, Moscow, Russian Federation

The authors present a case of mucopolysaccharidosis type VI in a child. Low incidence rate of mucopolysaccharidosis in pediatric population, its difficult differential diagnosis and treatment suggests that this description of the disease pathology and treatment with the analysis of errors and complications in an 11-year-old child would be of interest for orthopedists, neurologists, anesthesiologists, and pediatricians.

Keywords: mucopolysaccharidosis type VI, Maroteaux-Lamy syndrome, clinical course, diagnosis, treatment, case report

INTRODUCTION

Maroteaux-Lamy syndrome – mucopolysaccharidosis type VI (MPS) refers to a group of orphan diseases [1]. This pathology is caused by arylsulfatase B deficiency [2, 3, 4, 5]. In 1963, it was described by P. Maroteaux and E.J. Lamy as a separate nosological entity of MPS VI [6].

The diagnosis is confirmed by the biochemical determination of the defective enzyme [5, 7, 8]. The pathogenic enzyme replacement therapy (ERT) has been

possible since 2005 with the advent of Naglazyme (Galsulfase). In the Russian Federation, it appeared in 2009 [1, 8, 9, 10, 11]. Late diagnosis and late treatment of onset of MPS VI worsens the long-term prognosis [12].

The aim of the study was to describe possible errors and complications in the treatment of patients with MPS VI.

MATERIALS AND METHODS

Patient T., born in 2001, was admitted to the Central Institute of Traumatology and Orthopaedics (CITO) on 11 December 2012 with the diagnosis of MPS type VI and received medical treatment up to 28 August 2013. After thorough diagnostic work up the following disorders were found: stenosis of the spinal canal at the level of C1-C2; cervical myelopathy; spastic tetraparesis; left-sided thoracolumbar subcompensated scoliosis stage III; hydrocephalus; secondary cardiomyopathy with lesions of the right heart; insufficiency of aortic, tricuspid and mitral valves; bilateral conductive hearing loss; corneal clouding; megalocornea; pulmonary hypertension; chronic bronchitis; pneumosclerosis of the middle lobe of right lung; hepatosplenomegaly; and contractures of major and minor joints of the extremities. The height was 107 cm and weight was 24 kg.

The patient's parents are second-degree relatives. No pathology was revealed in the child at birth. At the age of 4 months, a restriction of the hip abduction was

revealed by an orthopedic surgeon and was considered as dysplasia of the hip joints. Patient was treated with an abduction splint for 4 months with no effect. Independent walking began at the age of 14 months. During the first 2 years of life the patient had several episodes of laryngitis, rhinitis, and otitis. Patient's facial features changed at the age of 3 years. At the age of 4 years, in the Regional Pediatric Clinical Hospital of Veliky Novgorod, MPS type VI was suspected, and the diagnosis was confirmed at the Medical Genetics Research Center of RAMS. Since the age of 5 years, delayed growth and the progression of respiratory disorders were observed. The patient received no pathogenetic therapy; instead, symptomatic treatment was administered. The parents noticed a decrease of motor activity at the age of 10: he could not walk independently more than 20 meters or 7–8 steps. At the age of 10 years, the patient began to walk with support. At the age of 11 years, the patient was examined at the Children's Health Research Center (from 17 September

Михайлова Л.К., Кuleshov А.А., Аржакова Н.И., Sokolova Т.В., Vetrile М.С., Shvachka I.V., Poliakova O.A., Gromov I.S. Maroteaux-Lamy syndrome–mucopolysaccharidosis type VI: a case report (errors and complications). *Genij Ortopedii*. 2017. T. 23. No 1. pp. 80-84. DOI 10.18019/1028-4427-2017-23-1-80-84.

ber 2012 to 26 November 2012). The diagnosis of MPS type VI was confirmed; a combined stenosis of the spinal canal at the level of C0-C1-C2 was revealed, and surgical treatment was recommended and the patient was referred to CITO.

On admission to CITO on 12 November 2012, the general condition of the patient was severe. He could not walk independently for the first year at CITO. The patient underwent the standard neurological examination, including the Frankel\ASIA scale assessment to determine the degree of spinal cord injury [13], an assessment of muscle strength on a 5-point scale of Nerve Injury Committee [14], and a clinical assessment of muscular spasticity on overcoming the muscular resistance to passive movements and the presence of pathological reflexes. The use of the Ashworth spasticity scale [15] and the 6-minute walk test (The Six-Minute Walk Test), used to examine patients with similar clinical manifestations of organs and systems [16, 17, 18, 19, 20, 21, 22], was impossible due to this patient's pronounced restriction of physical activity and the amount of passive movements in joints due to contractures. While assessing with the Frankel\ASIA scale assessment [13] indicated type C injury, indicating incomplete functional impairment of the spinal cord. Spastic tetraparesis with predominant lesions of the lower extremities was more severe on the left (upper extremities in the distal segments the muscle strength on the right was 4 points, and on the left it was 3 points; in the lower extremities in the proximal segments on the right it was 4 points, and on the left it was 3 points; and in the distal segments on the right it was 3 points, and on the left it was up to 2 points). Pathological wrist and feet reflexes were revealed. Spastic hypertension pre-

vented the patient from walking.

According to the results of the clinical examination and imaging, circular combined stenosis was diagnosed. In the craniovertebral junction, the spinal cord compression was 90% (**Fig. 1**) due to deposition of glycosaminoglycans in tissues. The medical consensus decided to perform decompressive intervention due to life-threatening condition.

When planning anesthesia, the severity of the child's condition was underestimated and the computer tomography of the lungs and trachea and EMG monitoring of the patient's condition was not performed. On 19 November 2012, the intubation was unsuccessful. The patient was transferred to the intensive care unit (ICU). Within 48 hours, respiratory failure occurred, which was associated with the underlying disease. The artificial lung ventilation (ALV) was initiated. On 23 November 2012, tracheostomy was performed. Due to cerebral edema and depression of consciousness to sopor, a single episode of generalized convulsions developed, and tetraparesis worsened to tetraplegia (type A on Frankel scale). After 14 days, active movements of the extremities gradually appeared, with maintenance of asymmetry (muscle strength up to 3 points in the hands, 3–4 points in the right lower extremity, 2 points in the proximal segment of the left lower extremity, and plegia of the left foot). ALV was used for the patient in the forced ventilation mode with support in volume.

After stabilization of the patient's status on 12 December 2012, the halo device was installed to immobilize the cervical spine, and resection of posterior half-arch of the C1 cervical vertebra and occipitospondylosclerosis were performed along with osteosynthesis with a titanium structure (**Fig. 2**).



Fig. 1 MRI (**a**) and CT with myelography (**b**) of the cervical spine of patient T. on admission to CITO. Stenosis of the spinal canal at the level of the craniovertebral junction C1–C2

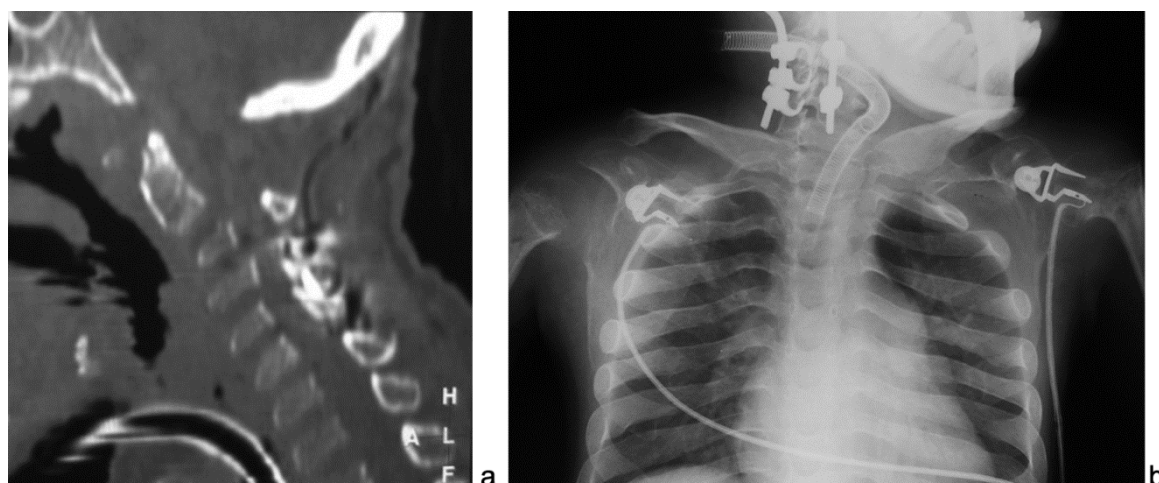


Fig. 2 CT of the cervical spine (a) and X-ray of the chest of patient T. (b) on the 3rd day after the imposition of the halo device, resection of posterior half-arch of the C1 cervical vertebra, occipitospondylodesis, and spinal decompression

The early postoperative period was complicated with liquor-dynamic disturbances and the worsening of spastic tetraparesis into tetraplegia. On 2 January 2013 ERT was administered, which included a weekly dose of Naglazyme 24 mg intravenously. After 3 months of ERT, a mild improvement in the nerve status was ob-

served: the emergence of active elbow flexion (up to 4 points), flexion/extension of fingers of both hands (up to 2 points), flexion/extension of the right leg at the hip and knee joints without the foot departing from the surface of the bed (2 points), and muscle tension of the left lower extremity (up to 1 point).

RESULTS

In July 2013, seven months after the surgery, the patient's status was of moderate severity and stable. The improvement of tetraparesis was observed: active tension of deltoid muscles appeared, the child bent and extended his elbows, made rocking motions with his hands within 20°, and bent and extended the fingers (2 points). The strength in the lower extremities increased by 1 point (up to 3 points on the right and 2 points on the left), which corresponded to type C on the Frankel scale. He sat in a wheelchair. The functions of the pelvic organs were maintained.

The regular ERT contributed to the improvement in respiratory system status: adjustable sputum viscosity and spontaneous breathing 12 hours a day. During the

whole treatment period in the CITO the patient was in the intensive care unit with ALV under constant monitoring of vital functions. The ALV mode was selected along with the control of the amount and quality of infusion therapy, ERT, symptomatic treatment, and rehabilitation.

On 28 August 2013, the patient was in a stable moderate condition and was transferred to the in-patient hospital in a primary care facility to continue the treatment. The child was in the intensive care unit of the CSTO, with continued ERT, and rehabilitation activities were performed. In the autumn of 2013, the patient developed nosocomial pneumonia, and died in November 2013.

DISCUSSION

A patient was diagnosed with MPS VI type at the age of 4 years. The lack of proper monitoring of clinical manifestations of Maroteaux-Lamy syndrome (delayed growth, multiple joint contractures, and decreased motor activity) and of adequate non-surgical treatment led to rapid disability of the child. Spinal stenosis was detected at the age of 10 years, but be-

fore admission to the CITO, ERT was not indicated for the child, which could have facilitated the postoperative period [23]. Surgical treatment at the CITO was undertaken due to severe cervical stenosis. Underestimation of the intubation complexity and a delayed ERT led to deterioration of the patient's condition.

CONCLUSIONS

Patients with MPS require close monitoring and MRI-control of the cervical spine at least two times a year.

Surgical treatment is possible after thorough examination and panel discussion of the patient's condition and obligatory ERT. EMG monitoring of the patient's condi-

tion is recommended. Computed tomography of the lungs and trachea in the preoperative period is indicated. Due to a difficult airway, the intubation requires the use of optical technology as follows: a fiberoptic bronchoscope, a laryngeal air-way, and a laryngoscope. The mucus vis-

cosity, which promotes lung atelectasis and paresis of intercostal nerves and diaphragm, makes the transfer of the patient from ALV to spontaneous breathing almost impossible, especially in cases of late detection of the disease and the treatment not being initiated in time.

REFERENCES

1. Novikov P.V., Semiachkina A.N., Voinova V.Iu., Zakharova E.Iu., Voskoboeva E.Iu., authors-compilers. Ministerstvo Zdravookhraneniia Rossiiskoi Federatsii. Federal'nye klinicheskie rekomendatsii po diagnostike i lecheniiu mukopolisakharidoza tipa VI [The RF Ministry of Health. Federal clinical recommendations for diagnosing and treating Type VI mucopolysaccharidosis]. M., 2013, 22 p. (In Russ.)
2. Kozlova S.I., Demikova N.S. *Nasledstvennye sindromy i mediko-geneticheskoe konsul'tirovanie: atlas-spravochnik. 3-e izd.* [Hereditary syndromes and medico-genetic consulting: atlas-reference book. 3rd Ed.]. M., T-vo nauch. izd. KMK, 2007, 448 p. (In Russ.)
3. Moller J.H., Hoffman J.I.E., eds. *Pediatric Cardiovascular Medicine*. Wiley & Sons, 2012, 1076 p.
4. Lachman R. *Taybi and Lachman's Radiology of Syndromes, Metabolic Disorders and Skeletal Dysplasias. 5th Ed.* Mosby, 2006, 1408 p.
5. Neufeld E.F., Muenzer J. The mucopolysaccharidoses. In: Scriver C.R., Beaudet A.L., Sly W.S., Valle D., eds. *The Metabolic and Molecular Bases of Inherited Disease. 7th Ed.* New York, McGraw-Hill, 1995, pp. 3421-3452.
6. Maroteaux P., Leveque B., Marie J., Lamy M. A new dysostosis with urinary elimination of chondroitin sulfate B. *Presse Med.*, 1963, vol. 71, pp. 1849-1852.
7. Novikov P.V. Lizosomnye bolezni nakopleniia - aktual'naia problema pediatrii i sovremennye vozmozhnosti patogeneticheskogo lecheniia [Lysosomal diseases of accumulation – a relevant problem of pediatry and current possibilities of pathogenetic treatment]. *Ros. Vestn. Perinatologii i Pediatrii*, 2014, vol. 59, no. 4, pp. 4-9. (In Russ.)
8. Horovitz D.D., De S. Magalhães T., Pena e Costa A., Carelli L.E., Souza e Silva D., De Linhares e Riello A.P., Llerena J.C. Jr. Spinal cord compression in young children with type VI mucopolysaccharidosis. *Mol. Genet. Metab.*, 2011, vol. 104, no. 3, pp. 295-300.
9. Grigor'eva V.N., Belova A.N., Rogozhkin S.B. Mielopatii i vozmozhnosti ee lecheniia pri mukopolisakharidozakh (obzor literatury i sobstvennoe nabludeniie) [Myelopathy and the possibilities of its treatment for mucopolysaccharidoses (review of the literature and the authors' own observation)]. *Nevrol. Zhurn.*, 2011, vol. 16, no. 3, pp. 10-17. (In Russ.)
10. Mikhailova L.K., Nechvolodova O.L., Kolesov S.V., Kuleshov A.A., Koryshkov N.A., Poliakova O.A. *Izuchenie mukopolisakharidozov v TsITO* [Studying mucopolysaccharidoses in Central Institute of Traumatology and Orthopaedics (CITO)]. *Priorovskie chteniia: sb. rabot Vseros. nauch.-prakt. konf.* [The Priorov Readings: Collection of the works of All-Russian Scientific-Practical Conference]. M., 2015, pp. 110-113. (In Russ.)
11. Pisariuk A.S., Lazarev P.V., Lobzhanidze T.V., Shavarov A.A. Mukopolisakharidoz VI tipa: mnozhestvennye vistseral'nye porazheniia i lechenie Naglazimom [Type VI mucopolysaccharidosis: multiple visceral involvements and treatment]. *Klinich. Farmakologiya i Terapiia*, 2014, vol. 23, no. 3, pp. 76-81. (In Russ.)
12. Buchinskaia N.V., Kostik M.M., Chikova I.A., Isupova E.A., Kalashnikova O.V., Chasnyk V.G., Gubin A.V., Riabykh S.O., Ochirova P.V. Skeletnye proiavleniia pri mukopolisakharidozakh razlichnykh tipov [Skeletal manifestations for mucopolysaccharidoses of different types]. *Genij Ortop.*, 2014, no. 2, pp. 81-90. (In Russ.)
13. Kirshblum S.C., Waring W., Biering-Sorensen F., Burns P.S., Johansen M., Schmidt-Read M., Donovan W., Graves D.E., Jha A., Jones L., Mulcahey M.J., Krassioukov A. Reference for the 2011 revision of the international standards for neurological classification of spinal cord injury. *J. Spinal Cord Med.*, 2011, vol. 34, no. 6, pp. 547-554.
14. Compston A. Aids to the investigation of peripheral nerve injuries. Medical Research Council: Nerve Injuries Research Committee. *Brain*, 2010, vol. 133, no. 10, pp. 2838-2844.
15. Belova A.N. *Neiroreabilitatsiia: ruk. dlia vrachei. 2-e izd.* [Neurorehabilitation: a guide for physicians. 2nd Ed.]. M., Antidor, 2002, 736 p. (In Russ.)
16. Solway S., Brooks D., Lacasse Y., Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. *Chest*, 2001, vol. 119, no. 1, pp. 256-270.
17. Gulmans V.A., Van Veldhoven N.H., De Meer K., Helders P.J. The six-minute walking test in children with cystic fibrosis: reliability and validity. *Pediatr. Pulmonol.*, 1996, vol. 22, no. 2, pp. 85-89.
18. Paap E., Van der Net J., Helders P.J., Takken T. Physiologic response of the six-minute walk test in children with juvenile idiopathic arthritis. *Arthritis Rheum.*, 2005, vol. 53, no. 3, pp. 351-356.
19. Moalla W., Gauthier R., Maingourd Y., Ahmaidi S. Six-minute walking test to assess exercise tolerance and cardiorespiratory responses during training program in children with congenital heart disease. *Int. J. Sports Med.*, 2005, vol. 26, no. 9, pp. 756-762.
20. Geiger R.R., Strasak A., Trembl B., Gasser K., Kleinsasser A., Fischer V., Geiger H., Loeckinger A., Stein J.I. Six-minute walk test in children and adolescents. *J. Pediatr.*, 2007, vol. 150, no. 4, pp. 395-399. e1-e2.
21. Swiedler S.J., Beck M., Bajbouj M., Giugliani R., Schwartz I., Harmatz P., Wraith J.E., Roberts J., Ketteridge D., Hopwood J.J., Guffon N., Sá Miranda M.C., Teles E.L., Berger K.I., Piscia-Nichols C. Threshold effect of urinary glycosaminoglycans and the

walk test as indicators of disease progression in a survey of subjects with mucopolysaccharidosis VI (Maroteaux-Lamy syndrome). *Am. J. Med. Genet. A*, 2005, vol. 134A, no. 2, pp. 144-150.

22. Harmatz P., Ketteridge D., Giugliani R., Guffon N., Teles E.L., Miranda M.C., Yu Z.F., Swiedler S.J., Hopwood J.J.; MPS VI Study Group. Direct comparison of measures of endurance, mobility, and joint function during enzyme-replacement therapy of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome): results after 48 weeks in a phase 2 open-label clinical study of recombinant human N-acetylgalactosamine 4-sulfatase. *Pediatrics*, 2005, vol. 115, no. 6, pp. e681-e689.
23. Harmatz P., Giugliani R., Schwartz I., Guffon N., Teles E.L., Miranda M.C., Wraith J.E., Beck M., Arash L., Scarpa M., Yu Z.F., Wittes J., Berger K.I., Newman M.S., Lowe A.M., Kakkis E., Swiedler S.J.; MPS VI Phase 3 Study Group. Enzyme replacement therapy for mucopolysaccharidosis VI: a phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human N-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study. *J. Pediatr.*, 2006, vol. 148, no. 4, pp. 533-539.

Received: 09.02.2016

Information about the authors:

1. Liudmila K. Mikhailova, M.D., Ph.D., Professor, *Priorov Central Scientific Research Institute of Traumatology and Orthopaedics* of the RF Ministry of Health, Moscow, Scientific Out-Patient Department; e-mail: cito-uchsovet@mail.ru
2. Aleksandr A. Kuleshov, M.D., Ph.D., *Priorov Central Scientific Research Institute of Traumatology and Orthopaedics* of the RF Ministry of Health, Moscow, Head of the Group of Vertebrology ; e-mail: cito-spine@mail.ru
3. Nadezhda I. Arzhakova, M.D., *Priorov Central Scientific Research Institute of Traumatology and Orthopaedics* of the RF Ministry of Health, Moscow, Head of Anesthesiology and Reanimatology Department
4. Tat'iana V. Sokolova, M.D., Ph.D., *Priorov Central Scientific Research Institute of Traumatology and Orthopaedics* of the RF Ministry of Health, Moscow ; e-mail: cito@cito-priorov.ru
5. Marchel S. Vetrile, M.D., Ph.D., *Priorov Central Scientific Research Institute of Traumatology and Orthopaedics* of the RF Ministry of Health, Moscow, Group of Vertebrology ; e-mail: cito@cito-priorov.ru
6. Irina V. Shvachka, M.D., *Priorov Central Scientific Research Institute of Traumatology and Orthopaedics* of the RF Ministry of Health, Moscow, Anesthesiology and Reanimatology Department ; e-mail: cito@cito-priorov.ru
7. Igor' S. Gromov, M.D., *Priorov Central Scientific Research Institute of Traumatology and Orthopaedics* of the RF Ministry of Health, Moscow, Group of Pediatric Vertebrology ; e-mail: cito-spine@mail.ru
8. Ol'ga A. Poliakova, M.D., *Priorov Central Scientific Research Institute of Traumatology and Orthopaedics* of the RF Ministry of Health, Moscow ; e-mail: beresklettt@gmail.com