Introduction

Multiple Mitochondrial Dysfunctions Syndrome type 3 (MMDS3) is an autosomal recessive severe neurodegenerative disorder that leads to loss of previously acquired developmental milestones. This usually occurs in the first months (or years) of life. The most common features are loss of motor function, spasticity, pyramidal signs, loss of speech, cognitive impairment, visual problems, and seizures. The disease course is highly variable - some patients die of respiratory failure early in childhood (or even infancy), whereas some survive but may be bedridden. Brain imaging assays show diffuse leukodystrophy in the subcortical region, brainstem, cerebellum, and spinal cord. Laboratory studies tend to show increased lactate levels and metabolic acidosis.

Genetics

MMDS3 is caused by pathogenic variants in the IBA57 (Iron-Sulfur Cluster Assembly Factor IBA57) gene. Most cases are de novo, while only a small percentage are inherited in an autosomal recessive manner. The protein encoded by this gene localizes to the mitochondrion and is part of the iron-sulfur cluster assembly pathway (the biosynthesis of mitochondrial 4Fe-4S proteins). Defects in this gene have been associated with autosomal recessive spastic paraplegia-74 and with multiple mitochondrial dysfunctions syndrome-3.

Clinical case

We present a 1-year-old male patient, born at term. Oxygen therapy was administered due to a mild perinatal asphyxia. The child had relatively normal psycho-motor development until 5 months of age when certain abnormalities were noticed – muscle hypotonia and loss of motor functions.

3 to 5 months old - muscle hypotonia, lack of postural control

At the age of 1 month – small for gestational age, perinatal asphyxia, failure to thrive.

6 months old, the child needs support in order to stay seated upright.
Brain MRI showed large areas of demyelination in the white cerebral matter. Additionally, we found increased lactate levels along with metabolic acidosis.

Whole exome sequencing showed two variants of uncertain clinical significance in the IBA57 gene: p.(Tyr108His) / p.(Gly318Ala19) which led to the diagnosis – MMDS3. The clinical course in this case was severe, leading to respiratory failure which warranted artificial ventilation. The patient was admitted to the ICU.

Conclusion
This constitutes the first Bulgarian case of MMDS3 – an extremely rare entity with highly variable clinical manifestations which require a multidisciplinary approach and close follow-up. The clinical course in our case was severe, which led to exitus letalis in 3 months after initial hospitalization.

Declarations
Authors have no conflicts of interest to declare. All pictures are used with the written consent of the child’s parents. No funding was received to assist with the preparation of this presentation.

References: