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Case Report

The first case of combined oxidative phosphorylation deficiency-1 due to a *GFM1* mutation in the Serbian population: a case report and literature review

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ABSTRACT

Background. Combined oxidative phosphorylation deficiency-1 (COXPD1) resulting from a mutation in the G elongation factor mitochondrial 1 (*GFM1*) gene is an autosomal recessive multisystem disorder arising from a defect in the mitochondrial oxidative phosphorylation system. Death usually appears in the first weeks or years of lifespan.

Case. We report a male patient with ventriculomegaly diagnosed in the 8th month of pregnancy. The delivery was done by caesarean section and respiratory failure occurred immediately after birth. Hypoglycemia, lactic acidosis, elevated gamma-glutamyl transferase and hepatomegaly were confirmed. The brain MRI detected hypoplasia of the cerebellar hemispheres, dilated lateral ventricles, and markedly immature brain parenchyma. Epilepsy had been present since the third month. At 5 months of age, neurological follow-up showed his head circumference to be 37 cm, with plagiocephaly, a low hairline, a short neck, axial hypotonia and he did not adopt any developmental milestones. A genetic mutation, a missense variant in the *GFM1* gene, was confirmed: c.748C>T (p.Arg250Trp) was homozygous in the *GFM1* gene.

Conclusions. To the best of our knowledge, 28 cases of COXPD1 disease caused by mutations in the *GFM1* gene have been described in the literature. COXPD1 should be considered due to symptoms and signs which begin during intrauterine life or at birth. Signs of impaired energy metabolism should indicate that the disease is in the group of metabolic encephalopathies.

Key words: elongation factor G1, mutation, hepatoencephalopathy, lactic acidosis, mitochondrial disorder.

Cellular bioenergetics relies heavily on the mitochondria, which operates the oxidative phosphorylation system (OXPHOS) to produce energy in the form of adenosine triphosphate. Through the numerous signaling pathways and cellular functions, mitochondria and OXPHOS, are involved in neuronal development, connectivity, plasticity and differentiation.[1] Malfunctions in the mitochondrial translation apparatus, stemming from mutations in either mitochondrial or nuclear DNA, have the potential to result in various mitochondrial-related disorders.[2] Coenen et al.[3] described two siblings, born to consanguineous parents, who died at 27 days and 5 months, and were found to have a severe defect in mitochondrial translation, reduced levels of OXPHOS and progressive hepatoencephalopathy (HE). A postmortem analysis indicated significant liver necrosis, corpus callosum hypoplasia, and widespread brain atrophy.

Combined oxidative phosphorylation deficiency-1 (COXPD1) is an autosomal

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recessive multisystem disorder resulting from a defect in the mitochondrial OXPHOS. In particular, COXPD1 is caused by a homozygous or compound heterozygous mutation in the G elongation factor mitochondrial 1 gene (*GFM1*). Instructions encoded in this gene guide the production of a mitochondrial translation elongation factor, specifically elongation factor G1 (EGF1). Hammarsund et al.[4] discovered and isolated the entire coding sequence of the human EFG (GFM1) gene on chromosome 3q25 and later authors mapped the *GFM1* gene to chromosome 3q25.1-q26.2. The GFM1 gene, encompassing 18 exons and spanning no less than 40 kb, is specifically involved in facilitating the translocation of peptidyl-tRNA from the ribosomal acceptor aminoacyl site to the peptidyl site once peptide bond formation has occurred.[5] The deficiency in the protein produced by GFM1 leads to a compromised capacity of the mitochondria to generate energy required for cellular functions.

COXPD1 is a severe, progressive disorder with variable manifestations and fatal outcome. The onset occurs soon after birth, and features may include growth retardation, microcephaly, spasticity, axial hypotonia, encephalopathy and liver impairment. Death usually occurs in the first weeks or years of lifespan.[2]

Here we describe the clinical features and diagnostic workup of a patient with neonatal hepatoencephalopathy due to recessive mutations in the nuclear gene *GFM1*, and compare these findings with other reports of this rare disease. To the best of our knowledge, a total of 28 patients have been reported so far, and this is the first case of COXPD1 due to a mutation in *GFM1* in a Serbian patient.

Case Report

Our patient is a 7-year-old male, born as the first child of young and healthy parents without consanguinity. Pregnancy was monitored regularly and in the 8th month of pregnancy ventriculomegaly was diagnosed by ultrasound (US) and then fetal brain magnetic resonance imaging (MRI) revealed unilateral left ventriculomegaly. The delivery was done by caesarean section due to the impending fetal asphyxia at 39 weeks of gestation. The birth weight (BW) was 3150 g, the birth length (BL) was 54 cm, the birth head circumference (HC) was 31 cm and Apgar score was 9/10. Hypospadias was observed during the physical examination. Due to respiratory failure immediately after birth, the child was transferred to the Department of Neonatology. A neurological examination at birth showed a dysmorphic face (hypertelorism and microcephaly). Hypoglycemia and lactic acidosis (LA) were detected in laboratory analyzes. Metabolic screening of urine and serum and genetic screening were normal. In laboratory analysis, there was an increased gamma-glutamyltransferase (γGT) of 217 IU/L, and the patient is currently being followed for hepatomegaly by gastroenterologists-hepatologists, even though liver enzymes were normal afterwards. After birth, the US of the central nervous system (CNS) showed that there was a dilated interhemispheric fissure, moderate dilation of the frontal horns bilaterally, wide plexuses, asymmetric, wide subarachnoid spaces, and poorly differentiated brain parenchyma. At that time, the brain MR verified marked expansion of the retrocerebellar space, hypoplasia of both cerebellar hemispheres, dilated lateral ventricles, and markedly immature brain parenchyma more prominent on the left. Since the third month, epileptic seizures have been present, which are understood as infantile spasms. The boy had about 30 seizures per day. Seizure semiology was an extension of his arms and legs, with a fixed gaze whereby the boy cries, all lasting only up to 10 seconds, and occasionally turns his head and eyes to the left side for a few seconds. The child also had multiple episodes of head-twitching with rapid blinking. Night attacks have occurred several times a year, and semiology corresponds to daytime seizures. After being transferred to another facility, phenobarbital and valproate were introduced into therapy, followed by transaminase and

γ-GT elevation. As a result, valproates were discontinued and phenobarbital was gradually reduced, leading to the normalization of liver enzymes. Echocardiography revealed a patent ductus arteriosus.

A control brain MR (at 4 months of age) revealed a decreased cerebral parenchyma volume, an expense of white mass (WM) with zones of gliosis, a dilated ventricular system and cerebellar hemisphere hypoplasia with partial vermis agenesis (Fig. 1).

At 5 months of age, neurological follow-up showed a HC of 37 cm, plagiocephaly, a low hairline, a short neck, and axial hypotonia, and he did not adopt any developmental milestones.

The control video electroencephalogram (EEG) examination confirmed the epileptic nature of the spasms but not the etiology. EEG revealed localized epileptiform changes bilaterally anteriorly at slow baseline activity. A hypsarhythmic EEG pattern was not recorded. Vigabatrin was introduced into therapy, and favorable but not complete seizure control was observed, which was the reason why lamotrigine was also introduced.

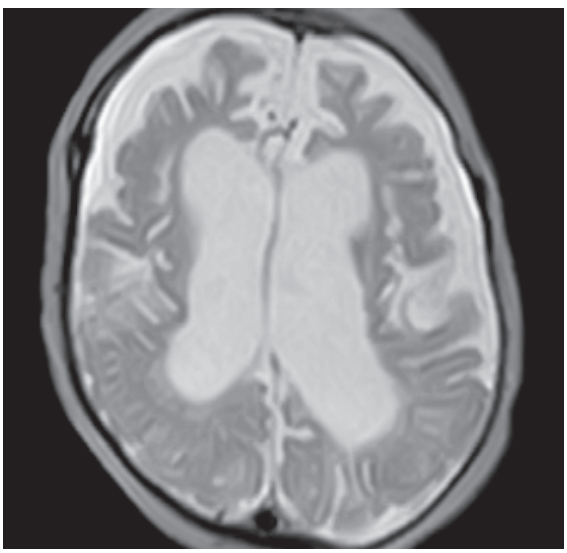

Fig. 1. Brain magnetic resonance imaging. Control brain MRI (at 4 months of age) demonstrating decreased cerebral parenchyma volume, the expense of WM, with gliosis zones and dilated ventricular system and cerebellar hemisphere hypoplasia with partial vermis agenesis.

The parents gave written consent for the publication of this case report.

Genetic findings

Due to respiratory weakness that existed at birth, LA, impaired liver function, seizures, pathological neurological findings, and slow psychomotor development, a metabolic disorder (MD) was suspected. With next generation sequencing, a homozygous missense variant in *GFM1*, was confirmed: c.748C>T (p.Arg250Trp), at 3q25.32. Both parents are asymptomatic carriers of the mutation. A diagnosis of neonatal mitochondrial disease was established. At the age of 3.5 years, he was again hospitalized for frequent seizures and slow psychomotor development. Neurological examination revealed, axial hypotonia and spastic tetraparesis, and it was noticed that he has not functionally adopted a single milestone. At the age of 4, he had pancreatitis, which was treated by antibiotics and symptomatic therapy (June 2019). The last control was in 2021, when it was concluded that there was no progression of the disease, the patient had unchanged neurological findings, and he did not have repeated epileptic seizures.

Discussion

Combined oxidative phosphorylation deficiency-1 disorder occurs as a consequence of a mutation in *GFM1* gene leading to impaired translation function in the mitochondria resulting in death in early childhood. Here we report a 7-year-old male patient with a homozygous c.748C>T (p.Arg250Tyr) mutation in *GFM1* gene. Since 2004, a total of 28 cases of children with a mutation in *GFM1* have been reported (Table I).

Most of the children were female (63.0%).[2,3,6-8,10-12,15] As in our case, consanguinity was not present in most cases (68.0%) [6-8,11,12,14,15], although both parents of our patient were healthy

Table I. The basic demographic and clinical characteristic of patients with GFMS mutations.

No	Reference	Year of publication	Consanguinity	Gender	Preterm birth	Onset of disease	Mode of birth	Death	Survival
1	Coenen[3]	2004	Yes	F[a]	NA[b]	*In utero*	C/S	Yes	27 d
2		2004	Yes	M[c]	Yes	*In utero*	NA	Yes	5 mo
3	Antonicka[6]	2006	No	F	No	*In utero*	NA	Yes	9 d
4		2006	No	F	Yes	*In utero*	C/S	Yes	45 min
5	Valente[7]	2007	No	F	No	7.d	NA	Yes	16 mo
6		2007	No	F	No	2.d	Ordinary	Yes	14 mo
7	Smits[2]	2011	Yes	F	No	2.d	Ordinary	Yes	2 yr
8	Balasubramaniam[8]	2011	No	F	No	*In utero*	C/S	Yes	8 mo
9	Galmiche[9]	2012	Yes	M	No	At birth	Ordinary	Yes	4 yr
10		2012	Yes	M	Yes	NA	C/S	Yes	20 mo
11	Calvo[10]	2012	NA	M	NA	1.wk	NA	NA	NA
12		2012	NA	F	NA	1.year	NA	No	NA
13	Brito[11]	2015	No	F	Yes	*In utero*	C/S	NA	NA
14	Ravn[12]	2015	Yes	M	No	*In utero*	Ordinary	Yes	4 mo
15		2015	Yes	F	No	*In utero*	Ordinary	Yes	14 d
16		2015	No	F	No	*In utero*	Ordinary	Yes	3 mo
17	Kohda[13]	2016	NA	NA	NA	NA	NA	NA	NA
18	Simon[14]	2017	No	M	Yes	3 mo	NA	No	7 yr
19		2017	No	M	NA	*In utero*	NA	Yes	10 mo
20	Barcia[15]	2019	No	F	No	At birth	Ordinary	No	9 yr
21		2019	No	F	NA	At birth	NA	No	2.5 yr
22		2019	No	F	No	At birth	Ordinary	Yes	3 yr
23		2019	No	M	No	8. mo	Ordinary	No	5 yr
24		2019	No	M	No	At birth	NA	No	2 yr
25		2019	No	F	No	At birth	Ordinary	No	16 mo
26		2019	No	M	No	At birth	Ordinary	Yes	9 mo
27		2019	Yes	F	No	At birth	Ordinary	No	15 mo
28		2019	No	F	No	At birth	Ordinary	No	5 yr

[a]Female [b]Not available [c]Male, C/S: Caesarean section

heterozygous carriers of the same mutation. Premature birth was reported in 20.0% of cases.[3,6,9,11,14] The birth of our patient was at the 39th week of pregnancy. The onset of signs and symptoms was most common in utero (38.5%)[3,6,8,11,12,14], but symptoms were also present at birth in 34.6%[9,15] during the neonatal period in 15.4%[2,7,10] and during infancy in 11.5%.[10,14,15] Intrauterine growth delay was observed in 10 cases.[2,3,6,8,9,12,14] All cases from the study by Barcia et al.[15] had parameters at birth that were either normal or within 1 SD. Our patient, born shortly before term and by caesarean section, had a normal BW, BL, HC, at birth. In a quarter of cases (27.8%), the pregnancy ended with a caesarean section[3,6,8,9,11], as in our case.

One patient from the study by Barcia et al.[15] was born without respiratory movements and was intubated for the first 6 hours.[15] Our patient was transferred immediately after birth due to respiratory distress syndrome. All of the published cases had slow psychomotor development. Other common elements of physical findings were spasticity of the arms and legs in 40.7%[2,3,7,9,11,12,14,15], microcephaly

in 37.0%[2,3,6,7,9,12], axial hypotonia in 37.0%[2,7,15], dystonic movements in 33.3%[9-11,15], a dysmorphic face in 25.9%[6-10,12,14], and feeding problems in 25.9%.[2,14,15] Spasticity of the arms and legs and axial hypotonia, which we also observed in our patient, were the most common neurological findings that have been reported in the published cases. Hypospadias at birth has been reported in 3 cases in the literature[9,12,14], as was the case with our patient.

Ten patients[2,10-12,14,15] had seizures, with 5 being diagnosed with West syndrome[15], 2 with infantile spasms[10,14], or evolution of Lennox-Gastaut syndrome.[2] Our patient had epileptic seizures from 3.5 months, and at 5 months, an EEG confirmed infantile spasms. In other cases, the EEG findings detected have been reported as follows: global, severe disorganization with complete lack of sleep spindles[7] or multifocal spikes and waves, without clear hypsarrhythmia[2] and multifocal polyspike paroxysms.[11] Initial therapy with phenobarbital and valproate in our patient resulted in an increase in transaminase values, so vigabatrin and lamotrigine were included. Bracia et al.[15] reported that they used a ketogenic diet, levetiracetam, vigabatrin, and hydrocortisone in West's syndrome therapy.

Our patient had a persistent ductus arteriosus, Antonicka et al.[6] also presented a patient who had a large ductus arteriosus. However, cardiac function is spared in this disease, and concentric left ventricular hypertrophy was shown in only one patient.[14]

Developmental delay was observed in all of the 19 patients in the literature[2,3,6-12,15], similarly our patient did not adopt a single developmental milestone. The most important and most common laboratory parameter was the elevated lactate (lactic acid) present in 21 patients[2,3,6-12,14,15], while 14 patients were reported to have acidosis (metabolic or lactic).[3,6-12,14,15] Although the disease is also known as neonatal mitochondrial HE[12], or infantile progressive hepatoencephalomyopathy[8], liver dysfunction has been reported in nine patients[3,9,12,13,15], while another four had hepatomegaly[2,8,14] and three cases had elevated transaminases.[7,8,14] Hypoalbuminemia[6,8,14] and coagulopathy[6,8,12] were reported in three patients each. Hypoglicemia[9,12] was observed in two patients, and one[8] had elevated γ-GT similar to our patient. Our patient had elevated transaminase levels due to phenobarbital and valproate therapy, but enzyme levels returned to normal after these two drugs were discontinued. Encephalopathy has been reported in 10 cases from the literature[2,3,7-10,15], although slow psychomotor development was present in all.

A change in signal intensity was verified on brain MRI in 13 patients.[7,8,11,15] For two patients, bilateral symmetric T2 enhancement and T1 decrease in signal intensity were revealed[7,8], while for three patients the authors did not specify what the change in signal intensity was.[7,11] An increase in T2 in the basal ganglia was detected in all patients presented by Barcia et al.[15] WM periventricular abnormalities[15] were shown in eight patients, ventricular dilatation in four[8,11,14,15] and thin corpus callosum in three patients.[2,11,15] Normal brain MRI on day 5 from birth for one patient was verified.[6] In our patient, decreased brain parenchyma volume, enlarged ventricular system, cerebellar tonsil hypoplasia, and partial vermis agenesis were revealed on MRI.

A fatal outcome was reported in 16 patients from the literature.[2,3,6,8,9,12,14,15] The mean age at death was 12.4 ± 13.8 months. For the 9 patients who were reported to be alive, the mean age was 4.1 ± 2.9 years[10,14,15] (data was available for 8). The oldest child who was reported to be alive was a 9-year-old girl.[15] In 4 patients, the same c.748C>T (p.Arg250Trp) mutation was present as in our patient[2,13,14] with only one patient being homozygous as our patient[2], and three patients (from two families) harbored the c.748C>T (p.Arg250Trp) mutation in compound heterozygosity with c.170C>A (p.Ser59Tyr) or c.689+908G>A (p.Gly230_231Glnins19).[13,14] There was no survival data available for

the patient presented by Kohda et al.[13] The patient who was homozygous for c.748C>T (p.Arg250Trp) passed away at 16 months of age[2], while one patient presented by Simon et al.[14] was 7 years old at the time of publication and the other who carried the identical combined heterozygous mutation died at 10 months. The longest survival of 9 years was reported by Barcia et al.[15] for a patient who had a combined heterozygote with the c.2011C>T (p.Arg671Cys) inherited from their father and the mutation c.1297_1300del (p.Asp433Lysfs*20) inherited from the mother.

We conclude that neonatal HE deserves special attention because of the symptoms and signs that begin during intrauterine life, either at birth or in the first few days of life. Signs of impaired energy metabolism (acidosis, respiratory problems, liver dysfunction, and encephalopathy) should indicate that the disease is in the group of metabolic encephalopathies. Additional features such as spasticity of the arms and legs, axial hypotonia, microcephaly, dystonic movements, a dysmorphic face, seizures, and MRI findings, such as changes in intensity of T1 and T2 signals, ventriculomegaly, could guide the testing process toward genetic analysis and this diagnosis.

Ethical approval

The parents gave written consent for the publication of this case report.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: DA MGJ, ST, MK, MB; data collection: DA, MGJ, ST, MK, MB; analysis and interpretation of results: DA, MGJ, ST, MK, MB; draft manuscript preparation: DA, MGJ, ST, MK, MB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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