BJMG 26 (2), 2023 • 59-64
DOI: 10.2478/bjmg-2023-0016
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CASE REPORT

EXPANDING THE PHENOTYPIC SPECTRUM: CHRONIC KIDNEY DISEASE IN A PATIENT WITH COMBINED OXIDATIVE PHOSPHORYLATION DEFECT 21

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ABSTRACT

Introduction

Pathogenic variants in *TARS2* are associated with combined oxidative phosphorylation deficiency 21 (COXPD21), an autosomal recessive disorder usually presenting as mitochondrial encephalomyopathy. Kidney impairment has been documented in a minority of COXPD21 patients, mostly with distal renal tubular acidosis.

Case report

We report on the first COXPD21 patient with generalized tubular dysfunction and early childhood progression to chronic kidney disease (CKD). Thorough diagnostic evaluation was initiated at six months of age due to failure to thrive, muscular hypotonia, motor delay and recurrent bronchiolitis. The boy was lost to follow-up until the age of two years, when he was readmitted with elevated creatinine level, reduced estimated glomerular filtrate rate, normochromic anaemia, metabolic acidosis and hyperkalaemia. Urine abnormalities pointed to generalized tubular dysfunction. Two novel heterozygous missense variants in *TARS2* gene were detected by the means of whole exome sequencing: c.1298T>G (p.Phe438Cys) of maternal origin and c.1931A>T (p.Asp644Val) of paternal origin. Currently, at 4.5 years of age, the boy has failure to thrive, severe motor and verbal delay and end stage of CKD. We referred the patient to paediatric centre that provides renal replacement therapy.

Conclusion

The overall clinical course in the patient we report on corresponds well to the previously reported cases of *TARS2* related COXPD21, especially in regard to neurological and developmental aspects of the disease. However, we point out the generalized tubulopathy and early occurrence of CKD in our patient as atypical renal involvement in COXPD21. Additionally, this is the first report of hypothyroidism and hypoparathyroidism in a COXPD21 patient.

Keywords: Mitochondrial disease; tubulopathy; *TARS2* gene

INTRODUCTION

Pathogenic variants in *TARS2* are associated with combined oxidative phosphorylation deficiency 21 (COXPD21), an autosomal recessive disorder most commonly presenting as mitochondrial encephalomyopathy (MIM# 615918) (1). The *TARS2* gene (MIM# 612805) encodes mitochondrial threonyl tRNA-synthetase. To the best of our knowledge, less than 30 patients of this particular mitochondrial disorder have been reported on to date (2,3). The main clinical features of COXPD21 include failure to thrive/growth retardation, developmental delay, axial hypotonia, hypertonus of the limbs, dystonia, seizures, and laboratory findings of lactic acidosis and elevated plasma alanine (1-4). Various pathological brain MRI findings have also been reported, such as high signal lesions in the basal ganglia and thalami, white matter volume loss, cortical atrophy, midbrain, and cerebellar atrophy (2,4,5). Metabolic crises are considered as potentially devastating

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aspects of COXPD21 (1). Early mortality was predominantly observed in children harbouring biallelic null mutations in the *TARS2* (3).

The prevalence of renal involvement in patients with primary mitochondrial disorders has been estimated to range from 25% to 50% (6). The most common renal phenotype in these patients is proximal tubulopathy with or without complete Fanconi syndrome, but a spectrum of manifestations has been described as well, including chronic kidney disease (CKD), distal tubular defects, focal segmental glomerulosclerosis, steroid resistant nephrotic syndrome, renal cysts, nephrocalcinosis and others (6-8). However, kidney impairment has been documented in only seven COXPD21 patients, presenting with distal renal tubular acidosis (2,4). A progress into chronic kidney disease (CKD) occurred in one patient at 17 years of age (4). Herein, we report the first COXPD21 patient with generalized tubular dysfunction and early childhood progression to CKD.

PATIENT REPORT

The patient is the first child of non-consanguineous parents (father has hypothyroidism and mother was treated for anxiety disorder), born from an uneventful pregnancy. Birth weight was 4.2 kg, and the perinatal period was normal. In early infancy, poor weight gain was observed. Thorough diagnostic evaluation was initiated at six months of age due to failure to thrive, muscular hypotonia, motor delay and recurrent bronchiolitis. The laboratory analyses revealed hyperlactatemia (2.53 mmol/l), hypokalaemia (2.8 mmol/l), absence of other electrolyte abnormalities in serum (table 1) and tubular loss of potassium and magnesium (table 2). The aldosterone level was normal. Serum creatine level and estimated glomerular filtration rates were normal at the time of the first evaluation. The ultrasound exam showed hyperechoic, normal sized kidneys.

After discharge he was lost to follow-up until two years of age when he was readmitted with an elevated creatinine level, reduced estimated glomerular filtrate rate, normochromic anaemia, metabolic acidosis and hyperkalaemia. Urine abnormalities pointed to tubular dysfunction (table 2). Aldosterone, renin and cortisol concentrations were within normal range, while decreased plasma concentration of parathyroid hormone (PTH) was accompanied by normal calcemia.

The association of chronic renal disease with developmental delay of unknown aetiology prompted genetic testing. Two novel heterozygous variants in the *TARS2* gene were detected by means of whole exome sequencing: c.1298T>G (p.Phe438Cys) missense variant derived from the mother and the c.1931A>T (p.Asp644Val) missense

Table 1. Key laboratory findings in serum/plasma over the course of the disease in a patient with COXPD21

Laboratory findings in blood	6 months of age	2 years of age	4.5 years of age	Reference range
Blood gases				
pH	7.4	7.39	7.42	7.35-7.45
HCO3m mmol/L	20.0	16.4	24.2	21-28
Base excess, mmol/L	-4.5	-8.5	-0.2	-2-+3
Biochemistry				
Serum creatinine, mcmol/L	24	111	274	23-37
GFR*, ml/min	116.4	32	17	≥90
Cystatin C, mg/L	1.16	2.22	4.5	0.62-1.2
Urea, mmol/L	4.9	15.0	35.0	3.3-7.5
Uric acid, mcmol/L	272	238	148	120-320
Potassium, mmol/L	2.8	6.8	5.8	3.4-4.7
Sodium, mmol/L	136	121	146	136-148
Calcium, mmol/L	2.71	2.27	2.38	2.05-2.74
Magnesium, mmol/L	0.88	0.67	0.90	0.7-1.05
Phosphorus, mmol/L	2.2	0.96	2.88	1.05-1.80
Lactate, mmol/L	2.53	2.15	2.0	0.2-2.0
Hormonal status				
Parathyroid hormone, pg/mL	26.3	3.3	17.5	15.8-68.3
25-hydroxyitamin D, nmol/L	47.8	58.9	18.0	75.0-250.0
Thyroid stimulating hormone, mIU/L	1.06	3.58	9.17	0.35-4.94
Free T4, pmol/L	16.63	12.7	8.98	9.0-19.0

*GFR – glomerular filtration rate

Table 2. Results of urinary analyses over the course of the disease in a patient with COXPD21

Urinalysis	6 months of age	2 years of age	4.5 years of age	Reference Range
pH	6.0	6.5	6.5	5-8
Urine- Specific gravity	1010	1010	1005	1010-1030
Urine protein, g/L	<0.1	<0.1	<0.1	<0.1
Urine glucose, mmol/L	Negative	Negative	5.5	Negative
Urine blood, RBC/uL	Negative	Negative	Negative	Negative
Urine white blood cells	Negative	Negative	Negative	Negative
Protein/Cr, mg/mmoL	20	30	52	<50
Aminoaciduria	Negative	Negative	Generalized	Negative
Beta-2 microglobulin/Cr, mg/mmoL	0.14	0.34	26.0	<0.35
Calcium/Cr, mmol/mmol	0.26	0.21	1.64	*
Uric acid/Cr, mmol/mmol	1.4	0.35	0.08	*
FeNa, %	0.8	3.1	32	<1
FeMg, %	6.65	4.98	38.4	<4
TTKG	9	3	2	4-6*
TRP, %	93.8	81.2	45	85-95
TmP/GFR, mmol/L	1.41	1.64	0.78	1.13-1.88

Cr – creatinine
FeNa – Fractional excretion of sodium
FeMg – Fractional excretion of magnesium
*TTKG – trans-tubular gradient of potassium (>4% suggests kidney losses in hypokalaemic patient; <7% indicate hypoaldosteronism in hyperkalaemia)
TRP – tubular reabsorption of phosphate
TmP/GFR - tubular maximum phosphate reabsorption per glomerular filtration rate
*Ca/Cr, mmol/mmol - (< 2.2 for <12 months; <1.5 for 1 to 3 years; <1.1 for 3 to 5 years)
*Uric acid/Cr, mmol/mmol - (1.5 for < 1 years; 1.3 for 1 to 3 years; 1.0 for 3 to 5 years)

variant derived from the father). At the age of 2.5 years the boy, was admitted due to generalized seizures associated with fever, severe metabolic acidosis and electrolyte imbalance (hyponatremia of 121 mmol/L, hypomagnesemia 0,5 mmol/L and hypophosphatemia 0,5 mmol/L). At the time he had elevated serum lactate (3.61 mmol/L). Pneumonia was verified, and during the treatment acute pancreatitis developed with hyperglycaemia requiring the insulin therapy. A moderate progression of chronic kidney disease was noted during this metabolic crisis (creatinine 164 mcmol/L) with subsequent polyuria. Urinary analysis showed persistent tubular dysfunction. The boy's overall condition deteriorated into encephalopathy. A brain MRI examination detected a pathologically increased signal of the brain parenchyma on T2/DVI/FLAIR sequences, in the projection of the basal ganglia, thalamus, hippocampus, substantia nigra, mesencephalic crus bilaterally, as well as in the posterior aspects of the pons and white matter of the cerebellum (figure 1). Mild supratentorial ventriculomegaly was described as well as a consequence of brain parenchyma reduction in the patient. An electroencephalogram showed diffuse slowing of basal activity of delta type without clear epileptic discharge. Slow recovery of neurologic functions ensued over the course of several weeks, while hyperglycaemia proved to be transitory, thus the insulin treatment was stopped.

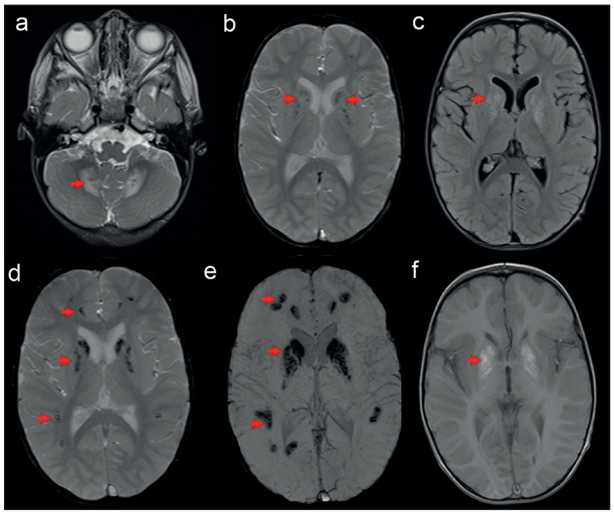

Figure 1. 1.5T Brain MRI of the patient: a-c were performed at the age of 2.5 years; a- pathologically increased signal of the brain parenchyma on T2/DVI/FLAIR sequences, in the projection of the white matter of the cerebellum; b- in the projection of nucleus caudate, globus pallidus, putamen and dentate nuclei there are punctiform and slightly linear zones of reduced signal intensity on the chemo-sensitive sequence, which are hyperintense on T1WI (c); d-f Brain MRI were performed at the age of 4 years; d- in the same regions, there are significantly larger hypointense signal lesions on T2WI/FLAIR sequences and SWI sequences (e), hyperintense on T1WI (f), corresponding to punctiform and serpiginous calcification zones. Mild ventriculomegaly is shown on these sequences.

Treatment during the disease included dietary modification, erythropoietin, calcitriol, ion-exchange resin, a "mitochondrial cocktail" of supplements and vitamins, and antiseizure medication. Thyroxine supplementation was introduced in response to hypothyroidism, detected at 4 years of age during a regular follow-up visit. Dosage of thyroxine had to be adjusted over time due to the worsening of thyroid function. Currently, at 4.5 years of age, the boy weighs 11 kg (below 3 standard deviations), has severe motor and verbal delay, and end stage CKD with generalized tubulopathy. We referred the patient to another paediatric centre that provides renal replacement therapy. The dynamics of the serum/plasma and urine laboratory findings during the course of the disease is presented in table 1 and table 2.

DISCUSSION

The clinical presentations of the patients we have reported on so far are mostly in accordance with other cases of COXPD21 (1-5.) The key clinical features of this particular mitochondrial disorder (failure to thrive, development delay, muscle tone abnormalities, epilepsy) are all present in our patient. A spectrum of brain MRI changes has been described in patients with COXPD21. Therefore, our patient's brain MRI scan revealed basal ganglia hyper intensity and generalized atrophy, resembling some of the more extensive findings thus reported (2,5).

Our report focusses on the renal aspect of a patient's phenotype, since the kidney's involvement in COXPD21 has been described in seven cases so far (2,4). In one of the reports, the male patient of Syrian descent presented with renal tubular acidosis, diagnosed at 6 months of age along with delayed psychomotor development (4). Nephrocalcinosis was observed at 12 months of age. In his early teenage years, the ultrasound showed small and scarred kidneys; the same patient was diagnosed stage III of CKD at 17 years of age. In the largest case series of COXPD21, a third of the patients had distal renal tubular acidosis (2). According to the data, none of them developed chronic kidney disease, despite half of them being of adult age. In contrast to previously reported patients, CKD was already present at two years of age and progressed into the end stage by the age of four. Moreover, the observed generalized tubulopathy differs our patient from COXPD21 patients with isolated renal tubular acidosis as the main tubular dysfunction. However, we can speculate that the origin of tubulopathy stems both from primary mitochondrial disorder and from advanced CKD itself.

Defects in the mitochondrial oxidative phosphorylation system are well-known genetic causes of renal dysfunction. Even though renal impairment can be the presenting feature of mitochondrial diseases, it is more commonly seen after the onset of neurological manifestations (9). Renal impairment can occur at any age in patients with mitochondrial disease, but the median age of this specific organ involvement has been estimated at 12 years (6). Typically, laboratory abnormalities of urine detected during regular patient check-ups are the first sign of kidney involvement in these patients. In our patient, at the very early age of six months, tubular loss of potassium and magnesium was verified. This indicated potential dysfunction of either thick ascending limb of the loop of Henle or distal tubule, even before the rise of urinary beta-2 microglobulin. Initially, there were no signs of proximal tubular dysfunction. Impairment of renal function was verified at two years of age in our patient and was consistent with both proximal and distal tubular dysfunctions. Full expression of Fanconi syndrome has been previously associated with mtDNA deletion syndromes, but also with diseases caused by nuclear DNA mutations affecting mitochondrial functioning (6,10). The presence of glycosuria, hyperphosphaturia, generalized aminoaciduria and low-molecular-weight proteinuria in our patient was detected at the end stage of CKD.

The progression of chronic kidney disease in our patient seemed to be facilitated during severe metabolic crisis occurring at the age of 2.5 years. Impairment of both proximal and distal renal tubules has been designated as generalized tubulopathy and described as such in several patients with mitochondriopathies (6). Interestingly, severe tubular dysfunction has been associated mostly with large mtDNA deletions, thereby contrasting to our patient's disease, caused by the autosomal-recessive mutations in nuclear *TARS2* gene. However, there have been reports of tubular impairment and chronic kidney disease in patients with mutations in *SARS2* gene which encodes mitochondrial seryl-tRNA synthetase (11). This autosomal recessive mitochondrial disease, caused by *SARS2* mutations, has been designated as HUPRA, an acronym based on the hallmarks of the disease (hyperuricemia, pulmonary hypertension, renal failure, alkalosis). Despite certain basic similarities in terms of abnormal mitochondrial protein translation in both HUPRA and COXPD21, clinical presentations of the two diseases are distinct. Renal impairment has been the hallmark of HUPRA, while only a quarter of COXPD21 cases published so far had kidney involvement. The patient presented herein is the second verified case of CKD in COXPD21. The overall clinical course is similar to that of our patient. Tubular dysfunction and early onset of CKD has been observed in several patients with mitochondrial genome mutations affecting tRNA synthesis (7,12). In a plethora of patients with respiratory chain assembly and function defects, kidney

involvement was noted as part of the multisystem disease, with proximal tubulopathy being the most commonly encountered renal phenotype (8).

The genotype of our patient includes two variants of unknown significance in *TARS2* gene detected by whole exome sequencing. After confirmation of combined heterozygosity of the proband, we performed a segregation analysis, proving carriership of single variants in the parents. Both variants we found in *TARS2* are designated as missense. According to one literature review of COXPD21 cases, carriers of biallelic missense variants in *TARS2* had later disease presentation with longer survival (3). However, a more recent study depicting 18 new patients with COXPD21 denied presence of any meaningful genotype-phenotype correlation (2). Although our patient had failure to thrive and delayed development early in infancy, his overall condition remained relatively stable over time, apart from one serious metabolic crisis at the age of 2.5 years. However, early and progressive CKD represents a key clinical feature in this particular patient, despite being non-typical for COXPD21.

The presence of hypothyroidism in our patient has been demonstrated by elevated thyroid stimulating hormone level and low free thyroxine in blood. A neonatal screening test for congenital hypothyroidism was previously negative. The level of thyroid peroxidase antibodies remained low, suggesting that the occurrence of hypothyroidism is most probably the part of the multisystem presentation of mitochondrial disease. Endocrine abnormalities represent one of the more prominent clinical features of mitochondrial diseases with hypothyroidism being present in approximately 6.3% of patients (13). Interestingly, defects in nuclear genes encoding mitochondrial protein pose a lower risk for hypothyroidism, when compared to mtDNA mutations (2.9% and 8.5%, respectively). The findings of the WES did not reveal any other genetic variant that could be causative to hypothyroidism. Hypothyroidism in the father is caused by Hashimoto thyroiditis and is most probably not related to the hypothyroidism in the proband. Subnormal levels of PTH found in context of overt CKD suggest hypoparathyroidism in our patient. Insufficiency of parathyroid secretion has been well established occurrence in mitochondrial disorders (14), but not in COXPD321 so far (2,3).

The overall clinical course in the patient we report on corresponds well to the previously reported cases of *TARS2* related COXPD21, especially in regard to neurological and developmental aspects of the disease. However, we point out the early occurrence CKD in our patient since it has been previously described in only a single case of COXPD21. The presence of overt hypothyroidism and hypoparathyroidism are additional phenotypic features that have not been reported on in patients with this specific mitochondrial disorder before. We hope that this case report will add to the deeper knowledge of the phenotypic spectrum of COXPD21.

AUTHOR'S CONTRIBUTION

Aleksandra Paripović wrote the manuscript and reviewed the literature. Nataša Stajić, Jovana Putnik, Slavica Ostojić, Biljana Alimpić, Nikola Ilić, Aleš Maver and Adrijan Saralija critically revised the contents and wrote specific parts of the manuscript. Aleksandra Paripović, Nataša Stajić, Jovana Putnik and Adrijan Sarajlija conceived the original idea and supervised the final draft.

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflict of interest.

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