www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2024;13(1):e130111
doi: 10.7363/130111
Received: 2023 Mar 29; revised: 2023 Aug 15; accepted: 2023 Aug 21; published online: 2024 Apr 30

Case report

New variant in the *FBXL4* gene – leading to mitochondrial DNA depletion syndrome

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Abstract

Defects in the mitochondrial DNA (mtDNA) cause mtDNA depletion syndrome (MTDPS), a subclass of mitochondrial disorders that are genetically and phenotypically heterogeneous. MTDPS is a rare autosomal recessive disease caused by a mutation of a nuclear gene named *FBXL4* (F-box and leucine-rich repeat protein 4), located on chromosome 6. This nuclear-encoded mitochondrial protein plays a vital role in mitochondrial bioenergetics, mtDNA maintenance, and mitochondrial dynamics. Pathogenic variants in the *FBXL4* gene reduce mtDNA synthesis, resulting in a large decrease in the mtDNA content in cells, which is essential for normal energy production.

These pathogenic variants in the *FBXL4* gene are associated with an encephalomyopathy MTDPS type 13 (MTDPS13), a rare and severe multisystemic disorder mainly characterized by infant-onset encephalomyopathy

and lactic acidosis, developmental delay, hypotonia with feeding difficulties and failure to thrive. Other features may include the central nervous system and the ophthalmologic, cardiac, gastrointestinal, genitourinary, and immunological systems.

Herein, we report the case of an infant born to consanguineous Pakistani parents with an early onset of severe lactic acidosis, hypotonia, feeding difficulties, hypertrophic cardiomyopathy, supraventricular tachycardia, and transient neutropenia harboring a homozygous variant in the *FBXL4* (c.370C>T [p.Q124*]) gene. This variant was identified in the patient's parents in heterozygosity. He started medical treatment (with coenzyme Q10, propranolol, and sodium bicarbonate) and multidisciplinary support. As a result, a progressive improvement in postural tone and feeding autonomy was observed during the first months of life.

Therefore, encephalomyopathy MTDPS13 should be suspected when dealing with patients with severe congenital lactic acidosis and developmental impairment.

Keywords

FBXL4 protein, lactic acidosis, DNA, mitochondrial, mitochondrial encephalomyopathies, congenital disorder, manifestations, neurologic.

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How to cite

Ferreira Gonçalves C, Lipari Pinto P, Claro AR, Coelho J, Quintas S, Rodrigues M, Costa P, Margalha Miranda A, Rebelo M, Nogueira C, Janeiro P, Gaspar A. New variant in the *FBXL4* gene – leading to mitochondrial DNA depletion syndrome. J Pediatr Neonat Individual Med. 2024;13(1):e130111. doi: 10.7363/130111.

Background

Mitochondria is a complex organelle found in almost all cell types of the human body. It performs various functions and is the critical site of energy production through oxidative phosphorylation [1]. It is under the control of mitochondrial genomes, and an adequate amount of mitochondrial DNA (mtDNA) is required to produce mitochondrial respiratory chain complexes.

Defects in mtDNA maintenance, caused by pathogenic variants in nuclear-encoded genes, are the origin of mtDNA depletion syndromes (MTDPS), a subclass of mitochondrial diseases with genetic heterogeneity. They are characterized by a significant reduction of mtDNA content in affected tissues due to defective mtDNA-encoded protein synthesis, which results in impaired oxidative phosphorylation, inadequate energy production, and multiorgan dysfunction [2-4].

MTDPS can be divided into at least four clinical subgroups, based on clinical presentation:

- hepatocerebral form, manifested by hepatic dysfunction, psychomotor delay, hypotonia, lactic acidosis, nystagmus and neurological dysfunction;
- myopathic form, with hypotonia, muscle weakness, dysarthria, dysphagia, and failure to thrive;
- encephalomyopathic form, whose main features are hypotonia, muscle weakness, psychomotor delay, sensorineural, hearing impairment, lactic acidosis and neurological dysfunction;
- and, finally, neurogastrointestinal form, with gastrointestinal dysmotility, weight loss, peripheral neuropathy, ptosis and neurological dysfunction [5].

FBXL4 (F-box and leucine-rich repeat protein 4), a nuclear DNA gene, encodes a specific protein that plays a vital role in mitochondrial bioenergetics, mtDNA maintenance, and dynamics. Pathogenic variants in the *FBXL4* gene are associated with a disturbance of the mitochondrial network, decreased activity of enzymes involved in mitochondrial energy metabolism, and depletion of mtDNA, leading to an encephalomyopathy MTDPS type 13 (MTDPS13) [4-6]. Analysis in tissues and cells of patients with this syndrome revealed a variably reduced mtDNA content and a normal or decreased activity of multiple complexes in electron transport chain activity [6, 7].

FBXL4-related encephalomyopathy MTDPS13 is a rare and severe multisystemic disorder mainly characterized by infant-onset encephalopathy, lactic acidosis, developmental delay, hypotonia with feeding difficulties, and consequent failure to thrive [8, 9]. Other less common features may include the central nervous system and the ophthalmologic, cardiac, gastrointestinal, genitourinary, and immunological systems [6, 8]. On neuroimaging, white matter

abnormalities and cerebral atrophy are commonly found [8]. Neonatal age is the typical presentation period, and a poor prognosis is seen in the vast majority of affected individuals, with progressive worsening of symptoms during the clinical course of the disease [1, 3].

Herein, we report the case of an infant born to consanguineous Pakistani parents with severe lactic acidosis, hypotonia, feeding difficulties, hypertrophic cardiomyopathy, and transient neutropenia harboring a homozygous variant in the *FBXL4* (c.370C>T [p.Q124*]) gene.

Written consent for publication was obtained from the parents.

Case report

This case describes a 2-month-old male, the first-born child of consanguineous Pakistani parents (second-degree cousins). Both family histories are negative for any neurometabolic disorders or developmental abnormalities, except for a first-degree maternal cousin with blindness and deafness without an identifiable cause. The pregnancy was only partially monitored in Portugal (initially followed in Turkey) and occurred without apparent complications. Due to fetal distress, the proband was born at 40 weeks via cesarean section. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively, and he had a low birth weight of 2,315 g (< 3rd percentile), length of 48 cm (between 3rd and 15th percentiles), and occipital-frontal circumference of 32 cm (3rd percentile), according to Fenton growth charts.

He was admitted to a Neonatal Intermediate Care Unit after birth due to recurrent and persistent hypoglycemia (minimum capillary blood glucose of 20 mg/dL at 2 hours after birth, treated with bolus and continuous infusion of glucose with a maximum infusion rate of 4.6 mg/kg/min) and severe feeding difficulties, requiring nasogastric tube. Additionally, a progressively worsening polypnea, without hypoxemia, was noted 8 hours after birth. First blood samples revealed the presence of severe metabolic acidosis (pH 7.02; pCO_2 17.8 mmHg; HCO_3- 9.1 mmol/L, reference range [RR] of 22-26 mmol/L; base excess -26 mmol/L; partially treated with sodium bicarbonate), hyperlactacidemia (maximum lactate level of 240 mg/dL, RR of 4.5-18), hyperammonemia (maximum ammonia level of 140 µmol/L, RR of < 100) and high values of ketonemia (1.6 mmol/L). Creatinine kinase (CK) was also elevated (1,504 U/L, RR 39-308) with a slight elevation of aspartate aminotransferase (AST) (49 U/L, RR 0-40). Alanine aminotransferase (ALT) value was in the normal range (12 U/L, RR 0-41).

On the 2nd day of life, he was transferred to a tertiary hospital's Neonatal Intensive Care Unit (NICU). For the suspected amino acid inborn error of metabolism, natural protein restriction was performed for 48 hours. On the 4th day of life, the metabolic acidosis (lactates went down to 106 mg/dL) and ammonia levels (values decreased to 51 µmol/L) improved, and natural protein intake was progressively reintroduced.

His first physical examination in the NICU showed a thin appearance, skin fold, hypospadias, right cryptorchidism, weak crying, and marked axial hypotonia (**Fig. 1** and **Fig. 2A**).

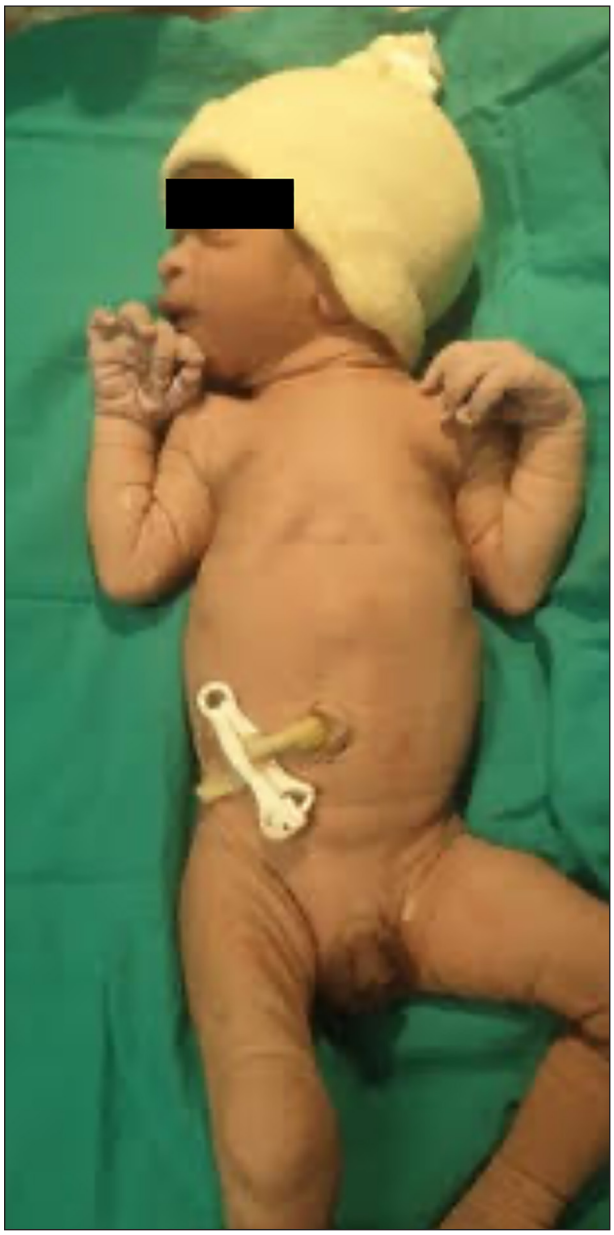

Figure 1. A picture of his first physical examination.

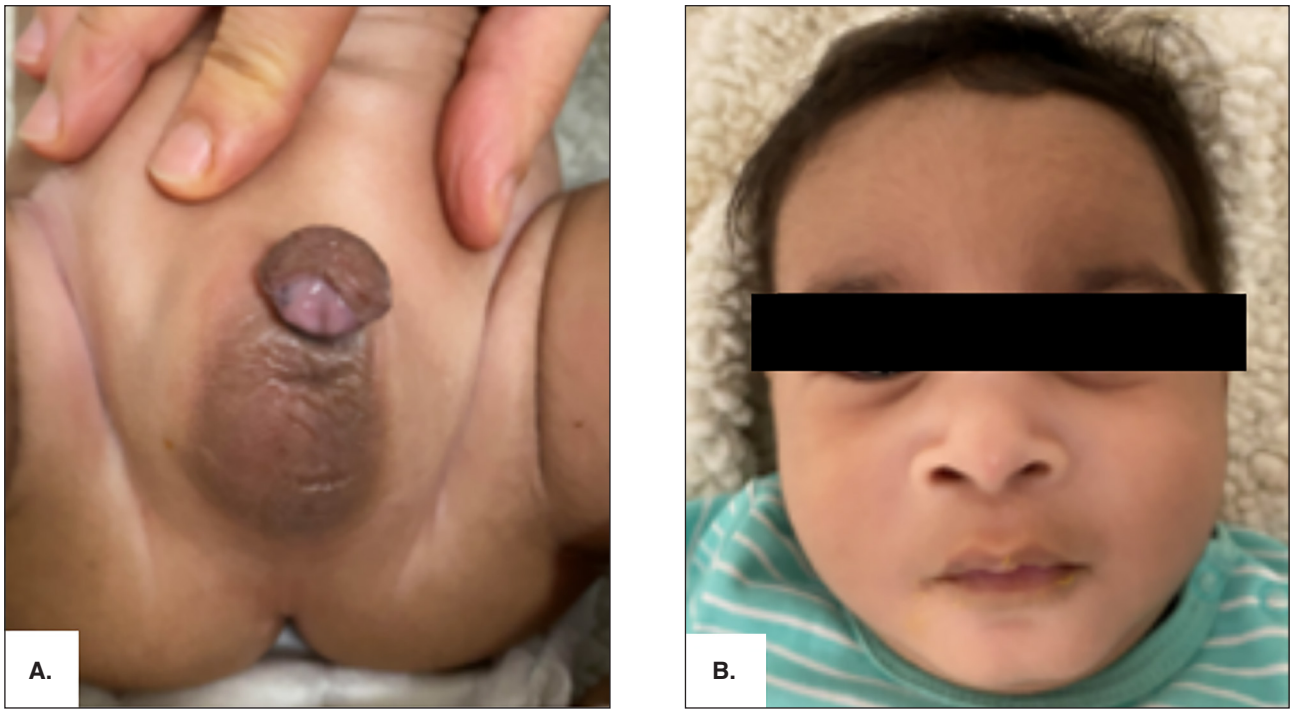

Figure 2. A. Hypospadias. **B.** Facial features of the child.

He did not have any dysmorphic features (**Fig. 1** and **Fig. 2B**).

In the initial complimentary assessment (3rd day of life), an echocardiogram revealed hypertrophic cardiomyopathy, an electrocardiogram and Holter showed supraventricular tachycardia (**Fig. 3**).

He started treatment with propranolol (initial dose of 0.5 mg/kg/dose), showing progressive improvement. Cerebral ultrasound revealed choroid plexus cysts and basal ganglia hyperechogenicity, and brain magnetic resonance imaging (MRI) revealed diffuse cerebral white matter edema, areas of restriction to diffusion in the posterior arm of the internal capsules and dorsal region of the trunk, consistent with the metabolic disorder (**Fig. 4**).

Taking into account the clinical picture and the blood results mentioned above, a metabolic investigation was performed in urine and plasma samples. Analysis in urine showed marked lactic acidosis and ketonuria. Analysis of amino acids in plasma revealed elevated levels of alanine (1,135.2 µmmol/L [RR 235.7-409.6]) and proline (881.1 µmmol/L [RR 98-254]), raising the suspicion of mitochondrial disorder. The acylcarnitine profile analysis was normal. In the several blood samples collected, transient neutropenia (with the lowest number of 490 neutrophils/mcL [RR 1,000-5,000]) was also noticed, without any infectious complication.

Next-generation sequencing of a combined mitochondrial and nuclear panel for the mitochondrial disease was requested, and a homozygous c.370C>T (p.Q124*) variant in the *FBXL4* gene was identified.

The patient's phenotype showed extensive overlap with encephalomyopathy MTDPS13, so the homozygous c.370C>T (p.Q124*) variant in the *FBXL4* gene was interpreted as the likely cause of the disease.

The heterozygous c.370C>T (p.Q124*) variant was identified in the patient's parents.

After the diagnosis of mitochondrial cytopathy, enzymatic cofactors (ubidecarenone at a dosage of 30 mg/kg/day and idebenone at a dosage of 15 mg/kg/day) were initiated.

During hospitalization, multidisciplinary support was given, including neurology, cardiology, nutrition, clinical metabolism, and medical genetics, occupational, physio, and speech therapies.

Ophthalmological evaluation, including funduscopic examination and otoacoustic emission, were all standard.

A progressive improvement in postural tone and feeding autonomy were observed during hospitalization, with no other new signs and symptoms, including seizures or movement disorders, which were previously described in patients with this diagnosis.

He was discharged at 1 month and 15 days of life, with complete feeding autonomy.

There were no other complications during hospitalization, and plasma lactate levels remained chronically elevated (79 mg/dL at the time of his discharge).

He maintained coenzyme Q10, propranolol, and sodium bicarbonate after discharge.

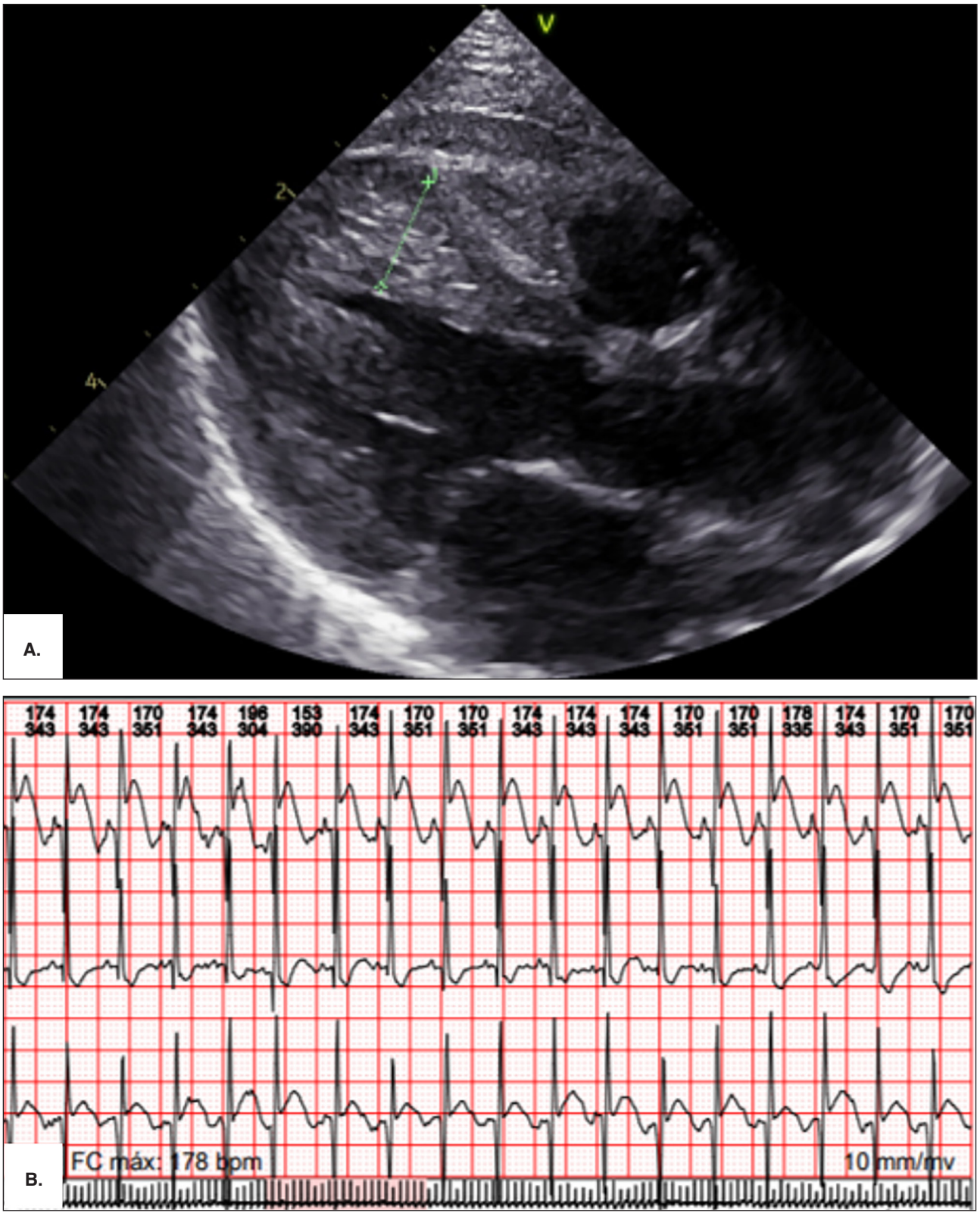

Figure 3. A. Echocardiogram images showing biventricular apical hypertrophic cardiomyopathy, without obstruction. **B.** Holter showing supraventricular tachycardia.

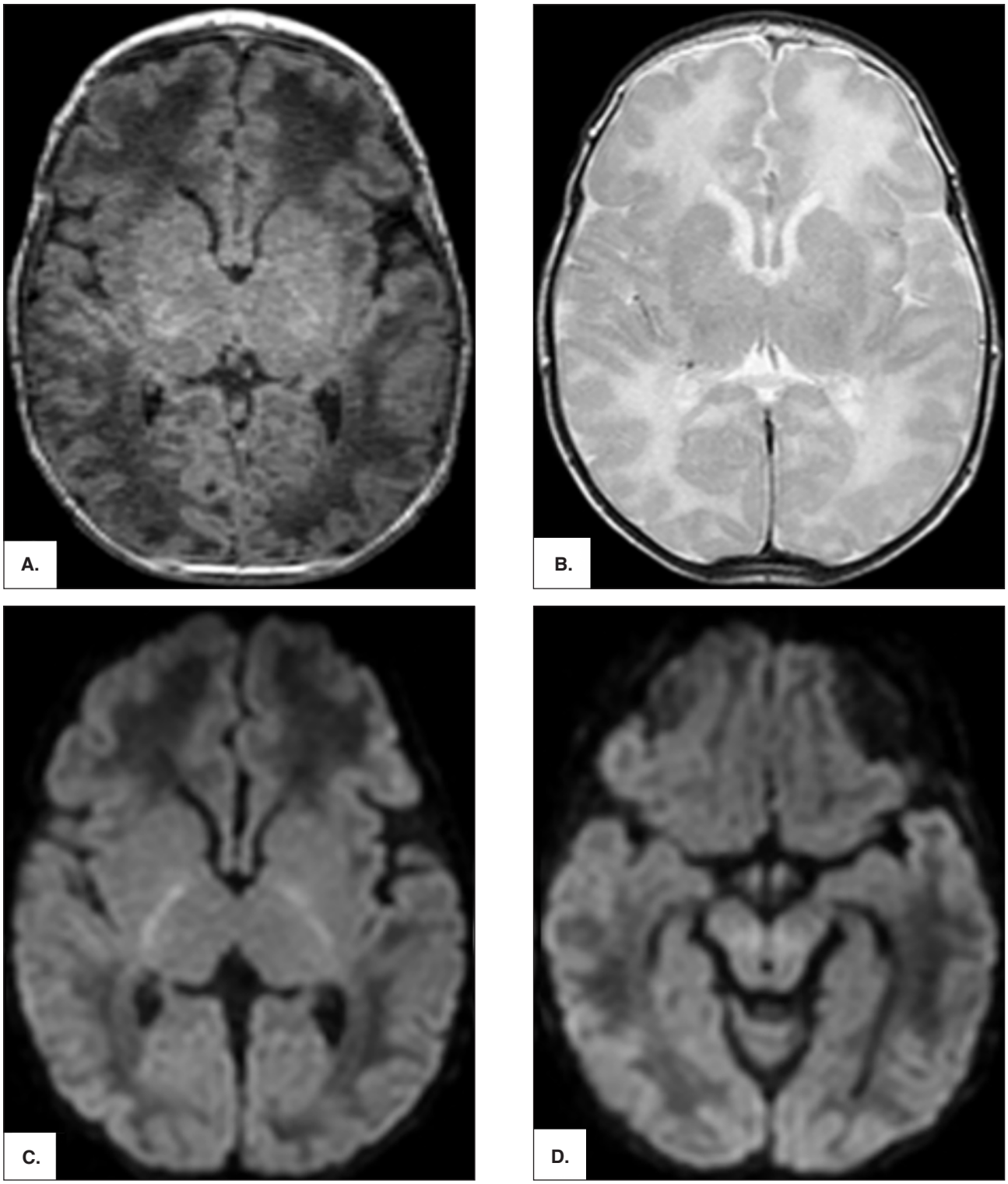

Figure 4. Magnetic resonance imaging (MRI) images revealing diffuse cerebral white matter edema (areas of hyposignal on T1 [**A**] with corresponding accentuation of hypersignal on T2 [**B**]), and restriction to diffusion in the posterior arm of the internal capsules and dorsal region of the trunk (**C** and **D**).

Discussion

FBXL4, located on chromosome 6, is a nuclear DNA that encodes a 621-amino acid F-box protein [1]. Although the precise *FBXL4* molecular function is yet to be fully discovered, it plays an important role in mitochondrial bioenergetics, mtDNA maintenance, and mitochondrial dynamics, including mitochondrial fusion and quality control [10-12].

It is known that biallelic pathogenic variants in the *FBXL4*, recognized since 2013, are associated with an encephalomyopathy form of MTDPS13 [3]. To date, more than 100 patients have been identified with *FBXL4* deficiency, and more than 60 pathogenic variants have been identified [6, 10, 12-24]. According to the work of El-Hattab et al., the majority of the variants are missense (51%) and nonsense (21%); in a minority of cases, they are frameshift (13%), splice-site (11%) and inframe deletion (2%) [6]. In our patient, a homozygous variant was discovered in the *FBXL4* gene. This is a frameshift variant caused by the insertion of a stop codon leading to loss of function and the presented phenotype.

The prevalence of *FBXL4* related to mtDNA maintenance defects is 1:100,000-400,000 [6]. It is estimated to be in 0.7% of the patients with mitochondrial disorders suspicion and 14% of those with congenital lactic acidosis [9]. The prevalence seems higher in the Arabs population compared to other ethnicities. The higher consanguinity rates in this group and a possible higher carrier status rate of *FBXL4* might explain this fact and are corroborated by the case presented herein [6].

FBXL4 MTDPS13 has a typical presentation during the neonatal period, but the age of onset can vary [14, 25]. At birth, more than half of the patients are small for gestational age showing the prenatal onset of growth failure [6]. Our patient showed this typical presentation. However, according to the literature, there is a great phenotypic variability between the affected individuals. Other prenatal and neonatal findings can involve the heart (hypertrophic cardiomyopathy, reported in 20%, and arrhythmia, reported in 12%), genital abnormalities such as cryptorchidism and hypospadias (reported in 20% and 16%, respectively), and bone marrow (neutropenia, lymphopenia), with an apparent susceptibility to infections, but in our case without any infectious complication, yet described [6, 8, 25].

Some distinctive facial features not seen in our case report are described in approximately 70% of affected individuals and may include prominent forehead and microcephaly, thick and diffuse eyebrows and synophris, short and upslanting palpebral fissures, broad nasal root with depressed nasal bridge, smooth philtrum, low set, and dysplastic ears [1, 8].

Neurologic manifestations (including seizures and movement disorders, such as dystonia, ataxia, and choreoathetosis), ophthalmological involvement (strabismus, nystagmus, optic atrophy, and visual deficit), and sensorineural deafness are described in less than one-third of the affected individuals, but might appear during the clinical course of this disease [6, 7, 19, 26]. In a minority of patients (less than 10%), other features are reported, including hypertonia, stroke-like episodes, pulmonary hypertension, impaired renal function, and renal tubular acidosis [6].

Typical biochemical findings are consistent with those of our patient. Elevation of blood lactate and alanine concentrations are universal, and blood ammonia might be mildly/highly elevated (ranging between 50 and 580 μmol/L), especially during intermittent episodes [6, 16, 27]. Liver transaminases are generally expected to be normal, but might be slightly elevated [27].

Brain MRI can show abnormalities in almost all individuals (93%), but there are no pathognomonic features. However, the two most common findings are abnormal white matter (70%) and diffuse cerebral atrophy (53%). The most common white matter abnormalities are bilateral diffuse T2 hyperintensity of subcortical and periventricular white matter and hypomyelination. Other exceptions include the involvement of basal ganglia, dilated ventricles, enlarged cisterna magna, corpus callosum thinning, periventricular cysts, and arachnoid cysts. MRI spectroscopy usually shows elevated lactate peaks [25].

There is no definitive treatment available to date. Thus, treatment is mainly supportive. The administration of vitamins, cofactors, respiratory substrates, or antioxidants, routinely used in mitochondrial disorders, can be started but is generally ineffective [22]. The use of dichloroacetate, an activator of mitochondrial pyruvate dehydrogenase complex, has shown to be effective in metabolic acidosis and reversed cardiac hypertrophy; it seems to improve neurologic and muscular function and mitochondrial physiology, mainly in mitochondrial dysfunction and altered morphology [10, 28].

Nutritional support is critical, as feeding difficulties are a significant problem and cause of morbidity. Most of the patients need nutritional support, even performing the use of a nasogastric tube or gastrostomy. Surprisingly, our patient's feeding difficulties were overcome during the hospitalization, and he was discharged with full feeding autonomy by mouth.

According to previous reports, most patients have a poor prognosis. Death is reported in about one-third

of affected individuals, with more than half dying during preschool. However, surviving individuals as old as 36 years have been reported [5]. The causes of death include multiorgan failure due to metabolic acidosis and infectious complications. The neurodevelopment function progressively deteriorates, and cardiac involvement, generally presenting as nonprogressive cardiomyopathy, can either be mildly progressive [22]. In a previous series of 21 patients, only 1 was considered to improve over time [25].

Follow-up should always be made by a multidisciplinary team, including specialists in neuropediatrics, nutrition, clinical genetics, metabolic medicine, developmental pediatrics and cardiology, among other professionals that might be needed [2].

Considering these prognosis and clinical courses, we should ensure regular multidisciplinary follow-ups with our patient. Our patient will maintain daily administration of coenzyme Q10, and other therapies will be initiated according to the clinical evolution. In addition, genetic counseling has been provided to these parents to guide future pregnancies since prenatal diagnosis, and preimplantation genetic testing is possible [8].

Conclusion

To the best knowledge, our patient constitutes the 106th case of *FBXL4*-related encephalomyopathy MTDPS13 reported to date in the literature. We describe a homozygous variant in *FBXL4* gene-related encephalomyopathy MTDPS13. It is a rare, severe multisystemic disorder that should be investigated when dealing with severe congenital lactic acidosis started in the neonatal period associated with neurological abnormalities. Besides the nonexistence of an efficacious therapy, the diagnosis allows an accurate prognosis and genetic counseling, and prevents patients from undergoing further diagnostic procedures. Due to the significant Arabs immigration that has been noted during recent years, European physicians must be aware of the existence of this syndrome when investigating patients suspected of having mitochondrial cytopathy.

More studies are needed to better understand the heterogeneity of population phenotype and the outcome of different genotypes.

Informed consent

Written informed consent was obtained from the parents.

Declaration of interest

The Authors declare that there is no conflict of interest. Financial support of the project: none.

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