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Unusual Presentation of Mitochondrial Depletion Syndrome Related to *FBXL4:* A Case Report

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Abstract

Background: Mitochondrial depletion syndrome (MDS) is phenotypically heterogeneous and may affect either single or multiple organs including muscles, liver, brain, and kidneys. *FBXL4*-related mitochondrial depletion syndrome of encephalomyopathic type is a severe condition that begins at an early age. It is primarily linked to brain dysfunction combined with muscle weakness.

Case presentation: In the present case, a homozygous loss of function variant of *FBXL4* (MIM 605654) was identified by whole exome sequencing (WES) in a three-year old Saudi girl who exhibited biochemical, and cerebral magnetic resonance imaging features consistent with mitochondrial DNA depletion syndrome 13, but had different presentations which has not been reported before.

Conclusion: MDTP13 (encephalomyopathic type) is caused by biallelic pathogenic variants in *FBXL4*. There is remarkable variability in genotype-to-phenotype correlation characteristic of this disease.

Keywords: *FBXL4* • mitochondrial DNA • Depletion Syndrome • Encephalomyopathic Type • Case Report

Introduction

Mitochondrial diseases have an estimated incidence rate of 1 in 5000 and account for a diverse range of genetically determined multisystem conditions that are characterized by a defective mitochondrial oxidative phosphorylation system [1]. One of them is mitochondrial depletion syndromes (MDS), which is an inherited autosomal recessive condition and can be detected in areas where consanguineous marriages are common and appears in various prognoses [2]. MDS can be divided into at least four clinical presentations namely; myopathic, encephalomyopathic, hepatocerebral and neurogastrointestinal. Encephalomyopathic MDS are caused by mutations in *SUCLA2*, *SUCLG1*, or *RRM2B that are usually present during infancy* [3].

F-Box and leucine rich repeat protein 4 (*FBXL4*) is a gene contains the N-terminal half of an F-box followed by 11 leucine-rich repeats which is observed in 1/13,005 chromosomes reported in the literature to date [1]. It is found in various organs including heart, kidneys, liver, lungs, pancreas, and placenta, but not in skeletal muscles, and maps to 6q16.1-q16.3 [1]. It is located within the intermembrane space in mitochondria of cell [4]. It plays a key role in the maintenance of mitochondrial DNA and homeostasis of mitochondrial bioenergetics including energy production, chemical signaling, cell growth control and proliferation and apoptosis [4]. Affected patients present at birth or in early infancy with a clinically heterogeneous group of disorders involving multiple organ systems including global developmental delay, hypotonia, persistent lactic acidosis, facial dysmorphism, congenital cataracts, and brain atrophy secondary to more than thousand nuclear genes contributing in mitochondrial function [5].

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A clinical case is presented which shows biochemical and molecular presentation of the FBXL-4-related mitochondrial DNA depletion syndrome (encephalopathic type) in a 3 years old girl of related Arabian origin family, who was present clinically different when compared with previous cases.

Case Presentation

A three-year-old Saudi girl was born full term, caesarean section due to premature rupture of membrane and fetal distress with APGAR score 6 at 1 minute and 8 at 5 minutes, to 35 years old mother, gravida 4, para 3 with no maternal illness. The patient's birth weight was 2.5 Kg, height was 50 cm and head circumference was 35 cm, which were all normal based on Saudi growth chart standard. She was admitted to the neonatal intensive care unit for 10 days due to persistent metabolic acidosis P^{H}= 7.294 (7.35-7.45), PCO_2=20.2 mmHg (35-45mmHg), base deficit=-15.9 mmol/L (-2 to 2 mmol/L), HCO_3=13.5 mmol/L (17-24 mmol/L) and a high lactic acid level 6.61 mmol/L (1.1-3.5 mmol/L), to rule out sepsis patient was treated by sodium bicarbonate and antibiotic. During this period, pediatric genetic consultation was done and was advised to get basic laboratory tests done, which were normal except microcytic anemia (Tables 1 and 2).

The tandem mass spectrometry (TMS) was normal. Urine dipstick for glucose and ketones were negative, while urine for reducing substance test, amino acid and organic acid were not available. It was recommended to continue sodium bicarbonate and the following were started; biotin, ubiquinone, riboflavin, and thiamin. As a part of initial diagnostic work up at birth, ophthalmological and hearing evaluation was done, which were normal. Furthermore, echocardiography showed patent foramen ovale (PFO), and moderate patent ductus arteriosus (PDA). Brain magnetic resonance imaging with intravenous contrast at age of one month revealed atrophic changes in the form of prominent intra- and extra-axial cerebrospinal fluid spaces, and abnormal dilatation of the perivascular spaces. Periventricular abnormal signal intensity with some restriction involving the hippocampus was also observed (Figure 1). The abdominal ultrasound showed mild left hydronephrosis.

The patient was discharged after normalizing the venous blood gas by

Table 1. Complete blood count.

Blood cell indices	Value	Reference
WBC	17.9 × 10^3/uL	(8.4-34 × 10^3 U/L)
Hemoglobin	10.7 g/dl	(14.5 g/dl)
Mean corpuscle volume	74.8 ft	(95 ft)
Platelets	353 × 10^3 uL	(192 × 10^3 U/L)

Table 2. Biochemistry including glucose, electrolyte, renal, liver and lipid profile.

Serum Biochemistry	Value	Reference
Glucose	53 mg/dl	40-63 mg/dl
Sodium	140 mmol/L	130-145 mmol/L
Potassium	4.23 mmol/L	3.7-5.9 mmol/L
Chloride	97.6 mmol/L	98-115 mmol/L
Magnesium	0.81 mmol/L	0.63-1.05 mmol/L
Calcium	2.35 mmol/L	1.9-2.6 mmol/L
Aspartate aminotransferase	41.9 U/L	47-15 0 U/L
Alanine aminotransferase	13.8 U/L	13-45 U/L
Total bilirubin	6.17 µmol/L	(<34 µmol/L
Direct bilirubin	0.553 µmol/L	(<10 µmol/L
Blood urine nitrogen	2.2 mmol/L	0.7-6.7 mmol/L
Creatinine	54 µmol/L	27-88 µmo/L
Cholesterol	114 U/L	20-200 U/L
Triglyceride	145 mg/dl	30-165 mg/dl
Low density lipoprotein	313 U/L	180-430 U/L
High density lipoprotein	58 mg/dl	34.6+_6.55 mg/dl
Ammonia	124 then 43 µmol/L	64-107 µmol/L
Lactate dehydrogenase	313 U/L	180-430 U/L

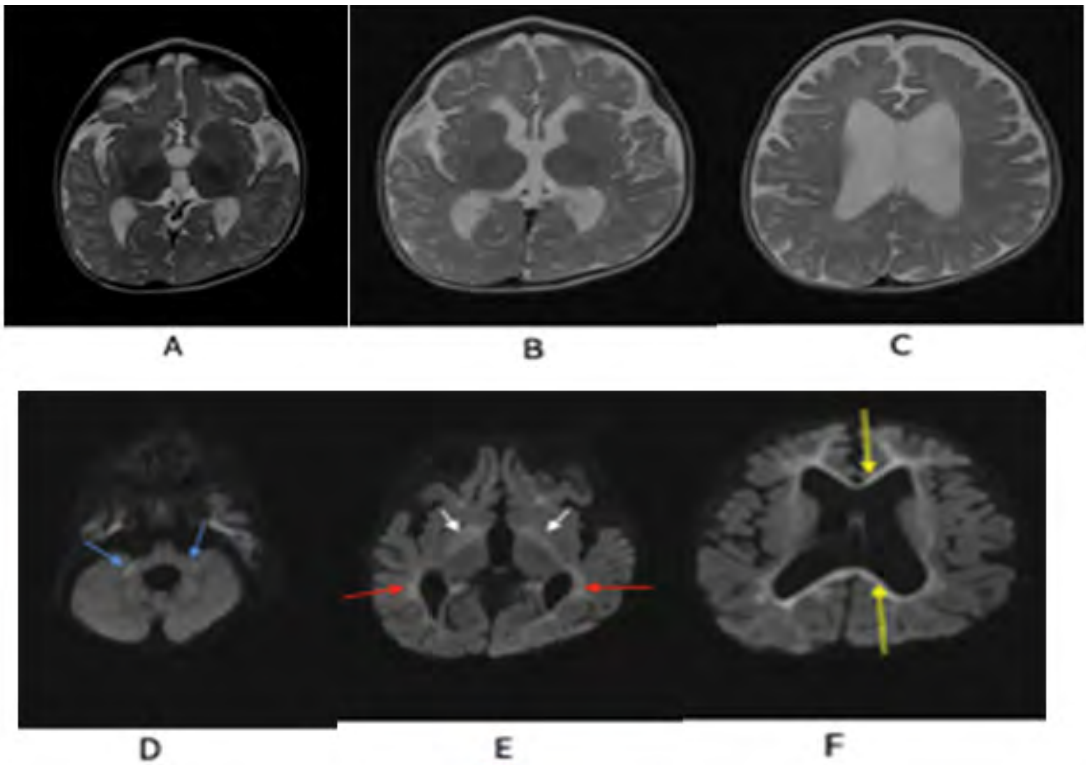

Figure 1. A 13-months-old baby girl. **(A-C)** axial T2 weighted images show brain atrophy and extensive T2 hyperintensity in globi pallidi, periventricular and deep cerebral white matter. **(D-F)** axial diffusion weighted images show reduced diffusion (hyperintensity) in middle cerebellar peduncles (blue arrows), globi pallidi (white arrow), corpus callosum (yellow arrows), periventricular and deep cerebral white matter (red arrows).

sodium bicarbonate and follow up was done with pediatric genetic consultant for further work up. At the age of one year, a generalized seizure disorder was developed and carbamazepine was started by neurology consultant, which was discontinued after 2 years of controlled convulsion and obtaining normal electroencephalograph (EEG).

The rate of admission to the hospital was 1–2 times per year due to metabolic crisis secondary to illness. The patient is the fifth child of related parents who were second-degree cousins (Figure 2). No family history of any neurological, metabolic, or developmental abnormalities was present.

During regular follow up physical examination revealed failure to thrive

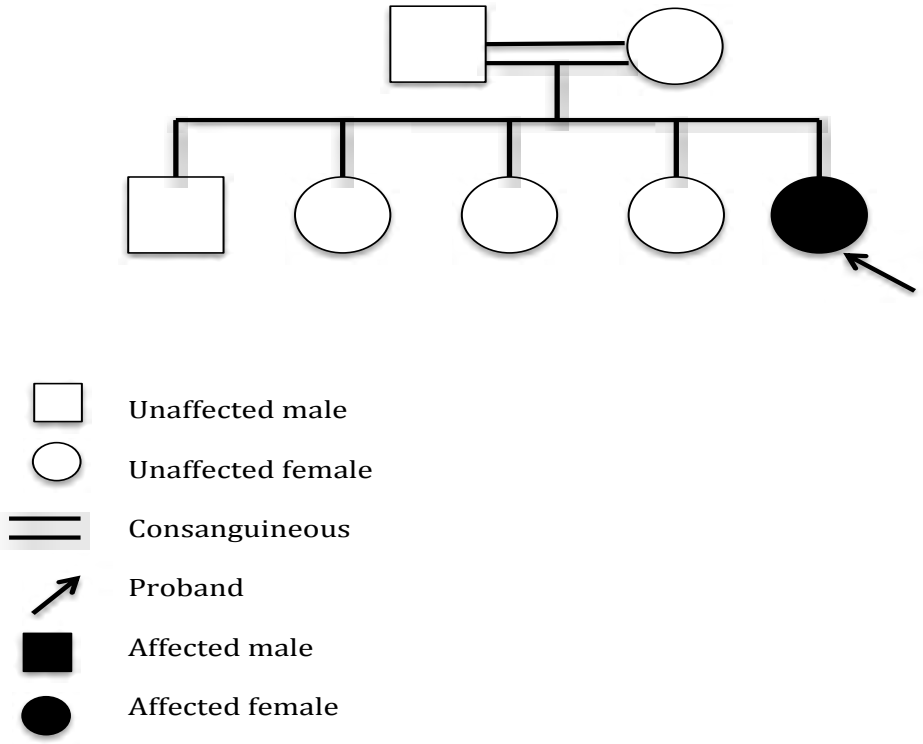

Figure 2. Family pedigree of a 3-year-old girl.

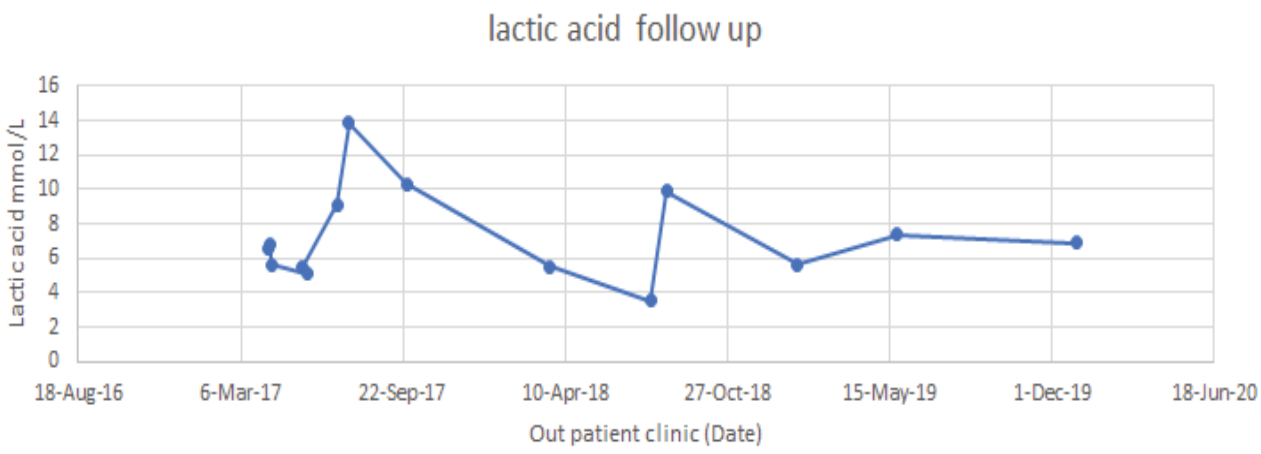

Figure 3. Trend of lactic acid over time.

Table 3. Comparison of our case manifestations to those of the three other patients reported with the same *FBXL4* genotype.

Variables	Our case	Ballout et al. (2019)	Bonnen et al. (2013) (S2)	Huemer et al. (2015) (Patient 13)
Sex	Female	Female	Male	Male
Age of symptom onset	At birth	3 months	Before 1 month	At birth
Age at presentation	1 day	9 months (severe anemia, mild leukopenia)	1 month	1 day
Birth weight (kg)	2.5	2.4	2.3	Unknown
Hypotonia	Severe	Severe	Severe	Severe
Cataracts	Absent	Absent	Present, with optic atrophy	Absent
Cardiac anomalies	Absent	None	Cardiomyopathy	Cardiomyopathy
Brain MRI findings	Brain atrophy in globi pallidi, callosum, periventricular, deep cerebral white matter and middle cerebellar peduncles	Bilateral temporal and frontal atrophy with non-hydrocephalus ventriculomegaly.	Prominence of the Cisterna Magna, with an abnormal appearance of the dorsal brainstem and posterior limb of the internal capsule.	Cerebellar hypoplasia
Lactic acid levels (mmol/L)	6.61	3.5	18	18
Ammonia levels	Non-elevated	Non-elevated	Non-elevated	Unknown
Age at death	3 years and still on follow up	*She was still alive at the age of 2 years and 8 months, after which she was lost to follow-up.*	4 months	Lost to follow-up

(weight = 10 kg, height = 85 cm, and head circumference was 45 cm at 3 years old, which were all below 3rd percentile according to Saudi growth chart), mild dysmorphism in the form of a triangular face, redundant skin, low set ears, and small chin. Also, there was kyphosis, generalized hypotonia, hyperreflexia, bilateral pes cavus, psychomotor delay and diffused muscle wasting. Also, she had profound motor and mental developmental delays that manifested as swallowing dysfunction, poor head control, inability to sit or roll over, and impaired speech development (developmental age was 3-4 months) while her age was 3 years. PDA and PFO were closed by itself after one year of birth, and hydronephrosis at age of 10 months was resolved without intervention.

The patient was referred to a tertiary hospital for simple whole exome sequencing at age of 16 months as the author's hospital did not offer this service. A homozygous loss of function variant of *FBXL4* (*FBXL4*:NM_012160:exone6:c.1303C>T:p.R435X) was identified and was reported previously as a disease-causing mutation in the Human Gene Mutation Database (HGMD), which is collated with all published gene lesions responsible for human inherited disease. This mutation is considered as pathogenic for mitochondrial-complex 1-deficiency mitochondrial deletion syndrome 13 (encephalomyopathy type). There was also a heterozygous variant of NDUFS1 (NDUFS1: NM_001199982: exon 12: c.1306C>G: p. L436V), whose role was unclear. After that, the family was counseled for sending sample from parents and siblings to confirm segregation and pre-implantation gestation diagnosis. She continued to follow up in outpatient department for controlling metabolic acidosis by sodium bicarbonate, where the degree of involvement of different systems were assessed comprehensively and symptomatic management was provided (Figure 3).

Discussion

Mitochondrial DNA depletion Syndrome is a group of genetic disorders caused by defects in multiple genes in mitochondrial DNA (mtDNA) maintenance. Among those is *FBXL4* mutation. To the best of author's knowledge, this patient represented the 95th case of Mitochondrial DNA Depletion Syndrome 13 (MTDPS13) related to pathogenic mutation in FBXL4 in a 3 years old Saudi girl worldwide [6]. Majority of this genotype were presented at birth with lactic acidosis, severe hypotonia, encephalopathy, epilepsy, kyphosis/scoliosis, cardiomyopathy, poor neurodevelopmental outcome, growth retardation, mildly craniofacial dysmorphic features, and mortality during infancy [7]. Whole exome sequencing showed this case had MTDPS13 with an underlying *FBXL4* mutation that had been reported in related individuals (c.1303C > T).

This article provides a comparison of the presented case with all *FBXL4*-deficient cases, which have been reported in the previous literature to act as a future mutation reference table for updates and association studies [6].

The present case was similar in presentation with Bonnen et al. but cardiomyopathy, signs, sensory-neuronal hearing impairment, cataract and optic atrophy were preserved [1]. On the other hand, expected survival time was extended more than infancy and had lower complications (anemia, leukopenia and hypoalbuminemia) like the case reported by Ballout et al. (Table 3) [6]. This emphasizes the remarkable variability in genotype-to-phenotype correlation characteristic of this disease. As MTDPS13 related to *FBXL4* (MTDPS13; OMIM # 615471) is autosomal recessive, stress is laid on the importance of offering families a prompt genetic counseling and pre-implantation genetic diagnosis (PGD) [4].

Conclusion

Hence, MDTP13 (encephalomyopathic type) is caused by biallelic pathogenic variants in *FBXL4*. Moreover, this case had various presentations clinically and is expected a survival. This should be considered as one of the differential diagnoses, especially by pediatric neurologists and geneticists for hypotonia and lactic acidosis in Saudi neonates, as its management involves a multidisciplinary team, including different specialists. However, more studies are needed to be conducted to better understand the heterogeneity of population phenotype and outcome of same genotype.

Conflict of Interest

The authors declare there is no conflict of interest.

Funding

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Consent of Publication

Consent for publication was obtained from the parents of the patient.

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