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CASE REPORT

Mitchell-Riley syndrome report of novel mutation and review of the literature

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ABSTRACT

Background: Mitchell-Riley syndrome (OMIM # 615710) is a rare autosomal recessive disorder, characterized by a genetic mutation in the *RFX6* gene. Clinically, it is presented with a triad of neonatal diabetes, gallbladder agenesis/hypoplasia, and intestinal atresia.

Case Presentation: We reported a female Saudi twin of consanguineous parents presented with neonatal diabetes, gallbladder agenesis/hypoplasia, and intestinal atresia since birth who deceased at 5 months of age due to sepsis. Molecular genetic testing of the *RFX6* gene showed novel homozygous missense mutation; NM_173560.3: (c.983A > T; p.Asp328Val). We compared the current patient to previously reported cases.

Conclusion: We alert the clinicians to consider this syndrome in any neonate presenting with diabetes, gallbladder agenesis, and intestinal atresia.

Keywords: Diabetes, RFX6 gene, Mitchell-Riley syndrome, gallbladder agenesis, intestinal atresia, pancreatic insufficiency.

Introduction

Mitchell-Riley syndrome (OMIM # 615710) is a rare autosomal recessive disorder characterized by a genetic mutation in the *RFX6* gene. The syndrome consists of neonatal diabetes mellitus with congenital digestive system defects including biliary atresia, pancreatic hypoplasia, duodenal and/or jejunal atresia, intestinal malrotation, gallbladder aplasia, and cholestasis (1,2). In addition, less common features were reported such as severe neonatal anemia (2–8), hypothyroidism (1,4,7), hemochromatosis (3,4,7), and anteriorly placed anus (8,9). Khan et al. (7) reported one case with atypical features of cerebral calcification, h ypospadias, and rhabdomyomas. Furthermore, heterotopic gastric mucosa in the small bowel and heterotopic pancreatic tissue were reported (2,6,8). Sansbury et al. and Skopkova et al. have described two siblings with the diagnosis of Mitchell-Riley syndrome with a milder phenotype. They had childhood onset diabetes and have survived post-infancy. The oldest child was reported alive at the age of 9 years compared with the usual poor prognosis of death within the first year of life in half of the cases (1–3,6,10,11). To date, there have been only 15 genetically confirmed cases reported with Mitchell-Riley syndrome (1–11). In this report, we describe a case with a novel mutation not described previously in the *RFX6* gene of an infant with Mitchell-Riley syndrome. The child presented with typical features including failure to thrive, neonatal diabetes, gallbladder agenesis, and intestinal atresia and deceased at 5 months of life due to sepsis. We compared the current case with the previously reported cases in the literature.

Case Presentation

Twin infants were a product of *in vitro* fertilization, second gravidity of a 33-year old woman with dizygotic (dichorionic, diamniotic) pregnancy, delivered to a consanguineous Saudi couple. The mother was diagnosed with diabetes mellitus at the age of 24, on oral medication, and was shifted to insulin therapy during her pregnancy. Antenatal ultrasound (US) showed normal Twin A, while Twin B had an abnormal gross anatomy of dilated bowel loop and polyhydramnios. They were born at 30 weeks of gestation by cesarean section due to premature labor and breech presentation. Twin A, a male infant born with APGAR scores of 8 and 9 at 1 and 5 minutes, respectively. He has normal growth parameters and physical examination was normal with no dysmorphic features. He had a smooth hospital course.

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He was discharged home with no complications noted after 20 days, mainly from his prematurity and low birth weight.

On the other hand, Twin B is a female infant scored an APGAR of 6 and 8 at 1 and 5 minutes, respectively. Weight at birth 1,100 g (10th–25th percentile), length 38 cm (50th percentile), and head circumference (HC) 28.5 cm (50th–75th percentile). No dysmorphic features were noted. She was shifted to the neonatal intensive care unit as she was initially requiring non-invasive mechanical ventilation; soon after she was intubated due to severe abdominal distention. Initial abdominal X-ray showed dilated bowel loop. X-ray with contrast was performed later which revealed a dilated stomach and first part of the duodenum with severe duodenal stenosis while the US reported an unvisualized gallbladder with collapsed distal bowel loops and rectum. Surgery was scheduled on the second day of life, but it was postponed as the patient was unstable due to severe coagulopathy, pulmonary hemorrhage, and uncontrolled hyperglycemia. Her hyperglycemia was noted from day 1. Four hours after birth blood glucose was 9.5 mmol/l (3.9–7.7mmol/l then started to increase reaching 23.7 mmol/l at 6 hours of life. She was requiring insulin infusion due to persistent hyperglycemia along with episodes of hypoglycemia. Her coagulopathy was completely resolved at the age of 4 days. During a hyperglycemic episode, insulin level was <2.0 µIU/ml (3.2–16.3 µIU/ml) and C-peptide 0.1 ng/ml (0.8–4.2 ng/ml) which were both low. Furthermore, there was no mutation in neither the *ABCC8* and *KCJN11* genes. Laparotomy was performed on day 17, confirmed duodenal and jejunal atresia along with Meckel's diverticulum. Additionally, a cyst-like lesion in the duodenum was resected and its histological study revealed the presence of heterotopic gastric mucosa. Feeding was initiated 10 days after surgery, but she was dependent on parenteral feeding as she failed to gain weight with a clay-colored watery stool. Medium chain triglyceride oil and trials of different formulas showed no improvement. Later on, cholestasis progressed with severe conjugated hyperbilirubinemia and was started on ursodiol. A hepatobiliary iminodiacetic acid (HIDA) scan reported non-visualized biliary channels. She had liver failure along with high ferritin levels 5,508 ng/l (4.6–204 ng/l) and transferrin saturation >48% suggesting a picture of hemochromatosis. At 2 months of age, her growth parameters showed a failure to thrive as follows: her weight 1.40 kg (<3rd percentile), her length 38 cm (<3rd percentile), and HC 30 cm (<3rd percentile). The repeated brain US showed a small right choroid plexus cyst while the echocardiogram study was normal. She underwent genetic analysis for the *RFX6* gene, which confirmed a novel homozygous missense variant not reported previously in the *RFX6* gene; NM_173560.3 (c.983A > T; p.Asp328Val), which causes amino acid, changes from aspartic acid to valine at position 328. The mutation was confirmed to be heterozygous in both parents and healthy sister while the wild type in a male twin.

Cholangiography and liver biopsy could not be performed as the patient condition was critical and deteriorated due to sepsis and passed away at the age of 5 months.

Discussion

The current patient is the 16th case ever reported of Mitchell-Riley syndrome in the literature, and the first case to be reported from Saudi Arabia and third from Arab ethnicity. The proband has the same classic phenotype features of Mitchell-Riley syndrome (Table 1), starting with classic features in-utero of intrauterine growth restriction, polyhydramnios, and duodenal atresia as well as the presence of key diagnostic features including neonatal diabetes, gallbladder agenesis, and intestinal atresia. However, the current patient lacked two major features, which are intestinal malrotation and abnormal pancreas. On the other hand, biliary atresia was suggestive by HIDA scan but could not be confirmed as she was not stabilized to undergo liver biopsy or cholangiography. Additionally, the current patient had malabsorption with chronic watery acholic stool, and exocrine pancreatic supplements were never given. Many reported cases with this mutation received a trial of exocrine pancreatic supplements but with no significant improvement (1–4,7–9,11). Similar to other cases, she had chronic anemia requiring multiple transfusions. Interestingly, heterozygous mutation in the *RFX6* gene was recently associated with maturity-onset diabetes of the young with reduced penetrance, which may have associations with the mother's diabetes as the mother was diagnosed with diabetes mellitus at the age of 24 years, on oral medication and, later on, shifted to insulin therapy during her pregnancy [12].

In 2015, Sansbury et al. (6) were the first to point out a new abnormal histological novel feature, where he reported the presence of heterotopic gastric mucosa in the small intestine. Later, Skopkova et al. (2) also described two cases with the same abnormal histological findings. All reported cases had a gastrointestinal bleed that improved after resection. Interestingly, this feature was found in the current case but she had no intestinal bleed. Amorim et al. (8), on the other hand, reported the presence of heterotopic pancreatic tissue.

Moreover, hemochromatosis reported in previous cases were found in the current patient (3,4,7). An additional feature that was never reported before, which could be an incidental finding in the current case was a small right choroid plexus cyst seen by head US. Pointing out, among all reported cases, brain pathology was only reported by Khan et al. (7), with periventricular calcification finding by brain magnetic resonance imaging (MRI).

For the first time in the literature, we reported a novel mutation that has not been previously reported (c.983A > T; p.Asp328Val) in the *RFX6* gene. The pathogenicity of this variant supported by segregation with other family members and the variant is rare and not described in the Exome Aggregation Consortium, Exome Sequencing

Table 1. *Summary of the clinical phenotype of previously reported cases compared to the current patient.**

		Sex	Ethnicity origin	Consanguinity	Birth weight (g)	Gestational age (weeks)	Onset of diabetes	Intestinal atresia	Histopathology	Intestinal malrotation	Meckel's diverticulum	Abnormal pancreas	Gall bladder	Biliary atresia	Hemochromatosis	Malabsorbtion	Chronic diarrhea	Pancreatic enzyme supplement	Cholestasis	Anemia	Other
Mitchell et al. (1)	1	M	Pakistani	+	1,540	36	Day 1	DA, JA	−	−	−	PH	GBA	IHA	−	+	−	+	+	NM	PFO, portal hypertension, esophageal varices
	2	F	Pakistani	+	1,310	34	Day 2	DA, JA	PVA	−	−	AP	GBA	IHA	-	+	+	−	+	NM	Hypothyroidism, esophageal varices
	3	F	Unknown	−	2,295	39	Day 2	DA, DW	−	+	−	Small	GBA	−	−	−	−	−	+	NM	Bilateral inguinal hernia
Chappell et el. (9)	4	F	Pakistani	+	1,700	35	Day 8	DA	−	+	−	−	GBA	−	−	−	+	+	+	NM	Anteriorly placed anus
Martinovici et al. (3)	5	M	Moroccan	+	1,340	38	Soon after birth	DA, JA	−	+	−	PH	GBA	+	+	+	−	+	+	+	NM
Smith et al. (10)	6	M	French	−	NR	35	Day 2	DA	−	−	−	−	−	−	−	−	−	−	−	NM	Gastrointestinal bleed
Spiegel et al. (4)	7	M	arab	−	1,490	38	Day 1	DA, JA	−	+	−	AP	GBA	−	+	+	+	+	+	+	Hypothyroidism, growth retardation
Concepcion et al. (11)	8	M	Vietnamese	−	1,375	34	Day 1	DA	−	+	−	AP	GBA	+	−	+	+	+	+	NM	NM
Chandra et al. (5)	9	F	West-Indies	+	1,390	35	Day 1	DS, JA	−	−	−	PH	−	−	−	−	+	−	−	+	NM
Sansubury et al. (6)	10	F	Turkish	−	1,650	32	3 years	DA, JW	HGM	−	+	−	GBA	−	−	−	−	−	−	−	Growth retardation, gastrointestinal bleed
	11	M	Turkish	−	1,700	34	6 years	DA	−	+	−	−	−	−	−	−	−	−	−	+	NM

(Continued)

		Sex	Ethnicity origin	Consanguinity	Birth weight (g)	Gestational age (weeks)	Onset of diabetes	Intestinal atresia	Histopathology	Intestinal malrotation	Meckel's diverticulum	Abnormal pancreas	Gall bladder	Biliary atresia	Hemochromatosis	Malabsorbtion	Chronic diarrhea	Pancreatic enzyme supplement	Cholestasis	Anemia	Other
Zegre Amorim et al. (8)	12	F	Portugal	+	1,370	35	Day 2	DA	HPT	+	−	AP	GBA	+	−	+	+	+	+	+	Anteriorly placed anus
Khan et al. (7)	13	M	Emirati	+	1,300	38	Day 2	DA	−	−	−	PH	GBA	−	+	+	+	+	+	+	Factor IX deficiency, hypothyroidism, hypertension, rhabdomyomas, hypospadias, Periventricular calcification
Skopkova et al. (2)	14	F	Caucasian	−	2,020	37	2 years	DA	HGM	−	−	−	GBH	−	−	+	+	+	−	+	Tubulointerstitial nephritis, growth retardation, gastrointestinal bleed
	15	F	Caucasian	−	2,700	39	2 years	DA	HGM HPT	−	+	AP	GBH	−	−	+	+	−	−	+	Gastro intestinal bleed
This report	16	F	Saudi	+	1,100	30	Day 1	DA, JA	HGM	−	+	−	GBA	+	+	+	+	−	+	+	Thrombocytosis, small right choroid plexus cyst
Total (%)	16			8/16 (50%)	<3 kg (100%)	Prematurity 10/16 (62.5%)	Neonatal 12/16 (75%)	100%	6/16 (37.5%)	7/16 (44%)	3/16 (19%)	9/16 (56%)	13/16 (81%)	6/16 (37.5%)	4/16 (25%)		10/16 (62.5%)	8/16 (50%)	10/16 (62.5%)	9/16 (56%)	

One male recently reported by Sangkhathat et al. (13) who described as part of cohort presented with biliary atresia and with no much information about another clinical phenotype.

AP = annular pancreas; DA = Duodenal atresia; DS = duodenal stenosis; DW = Duodenal web; GBA = Gallbladder agenesis; GBH = Gallbladder hypoplasia; HGM = Heterotopic gastric mucosa; HPT = Heterotopic pancreatic tissue; IHA = Intrahepatic atresia; JW = Jejunal web; JA = Jejunal atresia; NM = Not mentioned; PH = Pancreatic hypoplasia; PVA = Partial villous atrophy.

Table 2. *Prognosis and types of mutation in the previously reported cases compared to the current patient.*

		Prognosis	Genotype	Protein
Mitchell et al. (1)	1	Death at 5 months of age.	c.380 + 2T > C	-
	2	Death at 6 months of age.	c.380 + 2T > C	-
	3	Alive at 9 years, intermittently off insulin.	c.672 + 2T > G/c.224-12A > G	-
Chappell et al. (9)	4	Alive at 6 years, on an insulin pump, diabetes well controlled, thriving well, developmentally appropriate to age.	c.649T > C	p.Ser217Pro
Martinovici et al. (3)	5	Death at 2 months of age.	c.542G > A	p.Arg181Gly
Smith et al. (10)	6	Death at 2.5 months of age.	c.776_780 + 8del13	-
Spiegel et al. (4)	7	Alive at 1 year and 9 months, on insulin 0.7 U/kg/day, diabetes well controlled, HgA1c 7.1% persistent diarrhea on home TPN, moderate motor delay.	c.7812_787delAGGTTGA-TAinsG	-
Concepcion et al. (11)	8	Death at 5 months of age.	c.779A > C	p.Lys260Thr
Chandra et al. (5)	9	Alive at 6 years, on inulin 0.6 U/kg/day.	c.1517T > G	p.Val506Gly
Sansubury et al. (6)	10	Alive at 9 years, on insulin 0.35 U/kg/day, HgA1c 8.96%	c.2176C > T	p.Arg726*
	11	Alive at 9 years, on insulin 0.7 U/kg/day, diabetes well controlled HgA1c 7.2%	c.2176C > T	p.Arg726*
Zegre Amorim et al. (8)	12	Alive at 7 months, on an insulin pump with malabsorption. On home TPN.	c.541C > T	p.Arg181Trp
Khan et al. (7)	13	Not reported.	c.1153C > T	p. Arg385*
Skopkova et al. (2)	14	Alive at 13 years, on insulin 1.0 U/kg/day, diabetes well controlled, HgA1c 7.3%, developmentally well.	c.1154G > A/c.1316_1319delTCTA	p.Arg385Gln/P.Ile-439Thrfs*13
	15	Alive at 8 years, on insulin 0.95 U/kg/day, diabetes well controlled, HgA1c 6.9%, developmentally well.	c.1154G > A/c.1316_1319delTCTA	p.Arg385Gln/P.Ile-439Thrfs*13
This report	16	Death at 5 months of age.	c.983A > T	p.Asp328Val

Project, 1,000 genomes browser as well as a database of 2,000 in-house ethnically matched exomes. Additionally, computational analysis tools including polyphen, SIFT, and mutation tester predict this variant to be probably damaging. The molecular spectrum of the *RFX6* gene defect is heterogeneous. The most common type of mutation is missense accounting for 37.5%; however, other types of mutations including intronic, non-sense and deletion were reported. The genotype-phenotype correlation is unclear.

The prognosis of Mitchell-Riley syndrome is relatively poor with six cases (37.5%) having died in the first year of life (Table 2).

Conclusion

In conclusion, we report a case of Mitchell-Riley syndrome with a novel homozygous missense mutation. We alert the clinicians to consider this syndrome in any neonate presenting with diabetes, gallbladder agenesis, and intestinal atresia.

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The authors of this report have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Consent for publication
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Ethical approval
This study was approved by the Institutional review board office at King Abdullah International Medical Research Centre (KIMARC) (Study number: RC16/113/R).

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