Clinical management of Mitchell-Riley syndrome due to RFX6 gene mutations: aggressive support results in improved outcome

A. Poidvin(1), V. Chandra(5), AL Fauret-Amsellem(3), H. Cavé (2,3) , J.Beltrand(4,5) , N. Tubiana-Rufi(1), JC Carel(1,2), M. Polak(4,5), R.Scharfmann(5)

(1) Robert Debré University Hospital, Paediatric Endocrinologiy and Diabetology, Assistance Publique- Hôpitaux de Paris, Paris, France
(2) University Paris Diderot, Sorbonne Paris Cité, Paris, France
(3) Robert Debré University Hospital , Genetic Department, Assistance Publique-Hôpitaux de Paris, Paris, France
(4) Necker Universitary Hospital, Paediatric Endocrinology, gynécology and diabetology, Assistance Publique-Hôpitaux de Paris, Paris, France
(5) Inserm U1016, Institut Cochin, Paris, France

CONTEXT

Homozygous mutations in the transcription factor *RFX6* cause the Mitchell-Riley syndrome associating neonatal diabetes, pancreatic hypoplasia, gallbladder agenesis, duodenal atresia, and severe chronic diarrhea. Nine cases have been reported so far and the condition has a poor prognosis with five of nine patients who died before the age of 6 months.
We report here on the clinical management and outcome of two new cases from two independent families.

RESULTS

	Patient 1	Patient 2
Pregnancy and delivery	Severe SGA and duodenal atresia	Severe SGA and duodenal atresia
Family Background	Numerous cases of diabetes, with or without insulin. Some cases of milk intolerance. Parents first cousins, from a settled travellers family.	No cases of diabetes. Parents first cousins, from Martinique.
Birth weight (term) and sex	1290 g (37 weeks of gestation), M	1390g (35 weeks of gestation), F
Current age	2 years and 6 months	8 years
Diabetes		
Age at insulin initiation, modality, dose and HbA1c	1d, intra-veinous, pump since 6 months, 0.8 to 1 UI/kg/d, HbA1c <6%	1d, intra-veinous, pump from 3 to 19months old, then sub-cutaneous 0.6 UI/kg/d, HbA1c between 7 et 8,6%
Abnormal pancreas	Agenesis of tail and body	Hypoplasia of body
Digestive		
Malformations	Duodenal atresia, , gallblader agenesis, normal biliary tract. Hepatomegaly and splenomegaly, normal biliary tract.	Duodenal and jejunal atresia, gallblader agenesis, normal biliary tract
Complications	Moderate hepatic cytolisis (2 to 3 N) without cholestatic disease	Necrotising enterocolitis at day 50, fast for 3 months. No cholestatic disease.
Chronic diarrhea	Yes, even without enteral nutrition. Severe if enteral support > 50% of caloric intake	Yes, until the age of 12 months
Digestive histology	Normal	Normal
Parenteral nutrition	Yes, 100% of supplies, 10 hours/24	Yes until the age of 12 months. Weaning to a normal diet
Exocrine function	Normal fecal elastase	Normal fecal elastase
Hématology	No	Neonatal pancytopenia, spontaneous remission at day 7. G6PD deficiency. Chronic anemia requiring regular iron perfusion
Neurodevelopment	Slightly delayed	Presently normal
Growth	Presently at the mean for weight, -1 SDS for height	Presently at the mean for height, -1DS for weight
RFX6 Mutation	**Homozygous mutation exon 4 : c.541C>T (p.Arg181Trp) recently described in another family**	**Homozygous mutation exon 14 : c.1517T>G (p.Val506Gly) never described previously**

CONCLUSIONS

These patients demonstrate that an aggressive supportive management of patients with RFX6 mutations can result in an improved outcome in comparison with previous reports. The understanding of RFX6 role will open new therapeutic avenues, particularly the use of drugs that interfere with the gut endocrine system.

The authors have nothing to disclosure

References

1. Concepcion JP, Reh CS, Daniels M, Liu X, Paz VP, Ye H, et al. Neonatal diabetes, gallbladder agenesis, duodenal atresia, and intestinal malrotation caused by a novel homozygous mutation in RFX6. Pediatr Diabetes. févr 2014;15(1):67-72.
2. Zegre Amorim M, Houghton JAL, Carmo S, Salva I, Pita A, Pereira-da-Silva L. Mitchell-Riley Syndrome: A Novel Mutation in RFX6 Gene. Case Rep Genet. 2015;2015:937201.
3. Smith SB, Qu H-Q, Taleb N, Kishimoto NY, Scheel DW, Lu Y, et al. Rfx6 directs islet formation and insulin production in mice and humans. Nature. 11 févr 2010;463(7282):775-80.
4. Chandra V, Albagli-Curiel O, Hastoy B, Piccand J, Randriamampita C, Vaillant E, et al. RFX6 regulates insulin secretion by modulating Ca2+ homeostasis in human β cells. Cell Rep. 24 déc 2014;9(6):2206-18.

55ESPE 5--6-RFC
Management of Disorders of Insulin Secretion
Poidvin Amélie
DOI: 10.3252/pso.eu.55ESPE.2016
Poster presented at: ESPE 2016 PARIS