Martinez-Frias syndrome: Evidence of linkage to RFX6 mutation

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Abstract

Martinez-Frias Syndrome (MFS) is a rare disorder characterized as an autosomal recessive disease. It has been described as a disorder of duodenal atresia, extrahepatic biliary atresia, hypoplastic pancreas, intrauterine growth retardation (IUGR), and initially described with tracheoesophageal fistula. We present a case report of a preterm infant with a diagnosis of MFS, and a review of the literature. The constellation of symptoms described varies between the limited number of cases reported; this case presented is rare as the patient’s course was complicated by cerebral ischemia something not previously described.

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1. Case report

We report a case of a female neonate born with neonatal diabetes, neonatal hemochromatosis, gallbladder hypoplasia, hypoplastic pancreas, intestinal malrotation, and duodenal atresia. The patient is a female newborn with intra-uterine growth retardation (IUGR) delivered at 39–1/7 weeks gestation via spontaneous vaginal delivery to a 28-year-old mother who experienced an uncomplicated pregnancy. Routine ultrasound obtained at 18 weeks gestation was unremarkable; however, an ultrasound obtained on the day of delivery revealed polyhydramnios.

The patient’s birth weight was 1400 g, and initial examination revealed that the sternum was noticeably short, ending 1 cm below the nipple line with a prominent rib cage. Subsequently the patient was noted to be alternatingly hypoglycemic and hyperglycemic and also anemic (hemoglobin 7.9 g/dL). The anemia was treated with a red blood cell transfusion. Abdominal X-rays were obtained secondary to distention and a bluish hue over the abdominal wall, which demonstrated a “double bubble” sign suggestive of duodenal atresia. Exploratory laparotomy demonstrated duodenal atresia and intestinal malrotation without volvulus. The patient underwent a Ladd’s procedure along with creation of a duodeno-duodenostomy. Postoperatively, the patient was transferred back to the NICU intubated without evidence of complication.

On POD 1, the patient was noted to have no spontaneous movements. A non-contrast head CT revealed multifocal areas of attenuation suggestive of ischemia involving the cerebellar vermis, both cerebellar hemispheres, midbrain, and both thalami (Fig. 1). Further work-up included an EEG, which revealed seizure activity most consistent with diffuse encephalopathy. MRI revealed multiple foci of acute ischemia in the infra- and supra-tentorial brain consistent with hypoxic ischemic encephalopathy. MRA revealed multilevel occlusion of the internal carotid and basilar arteries; however, the MRA was grossly normal without evidence of large vessel occlusion (Fig. 2). Despite extensive work-up the etiology of the stroke was not identified prior to death. Factor V
and factor II were examined and were negative, with no evidence of a hypercoagulable state. On the tenth day of life, assisted ventilation was withdrawn and the patient expired 2 h later secondary to respiratory failure. Permission for autopsy was granted.

Autopsy performed revealed a duodenal atresia (Fig. 3), intestinal malrotation, and a very short wide based Meckel’s diverticulum, which had been noted intraoperatively. Findings also included a hypoplastic pancreas with non-functional islets, gallbladder hypoplasia, and neonatal hemochromatosis (Fig. 4). Immunohistochemical analysis revealed 4+ positive iron staining. Examination of the brain post-mortem was consistent with a hypoxic-ischemic event; there was also evidence of an ongoing hypoxic-ischemic process; the etiology of the ischemic event was unidentified.

2. Discussion

We report a case of Martinez-Frias syndrome, an autosomal recessive genetic disorder that was initially reported in 1992 [6]. The patient, a female born to unrelated parents, suffered from duodenal atresia, polyhydramnios, IUGR, a hypoplastic gallbladder, and intestinal malrotation, all of which have been associated with MFS in previous reports [1–6].

Microarray analysis of this patient demonstrated multiple regions of homozygosity equivalent to 3.4% of her genome. The region of homozygosity began at band 6q15 and extended to 6q22.33. This region contains the RFX6 gene, a gene that has been associated with MFS [1]. This gene has been linked to neonatal diabetes along with loss of stomach, lung, and pancreas tissue. It is also a member of the regulatory factor x family of transcription factors. Murine studies have revealed that this gene is specifically required for the differentiation of islet cells for insulin production, and it regulates the transcription factors involved in beta-cell maturation and function [5,7]. The gene is also noted for its involvement in gut development and function, along with neonatal diabetes [5,7]. Considering the symptoms attributed to mutations in the RFX6 gene, the patient’s homozygotic region may have been responsible for her anatomic and endocrine abnormalities.

In 2004 Mitchell et al. described a disorder involving a hypoplastic pancreas, intestinal atresia, gallbladder atresia, and neonatal diabetes making this a separate disorder from MFS [8]. Cases reported with RFX-6 gene mutations have features consistent with both MFS and those reported by Mitchell et al. [8,9]. Considering RFX6’s involvement in at least one prior case of MFS, it must be considered that MFS and the disorder characterized by Mitchell are variations of the same syndrome. This data supports the idea that RFX6 testing should be considered in patients with this phenotype.

The large profile of symptoms for MFS can be attributed to its recent discovery and limited number of case reports. This patient suffered from several ailments classically associated with MFS, but her case is remarkable for an ischemic stroke, which led to her death. The etiology of the stroke remains uncertain.

3. Conclusion

MFS is still not fully characterized at this time as the full constellation of symptoms involved remains to be described and may include cerebrovascular accident. The possible connection with the disorder described by Mitchell et al. has yet to be
Further analysis of future patients with classic MFS along with variations of the disorder and the RFX-6 gene is still required to fully understand this syndrome.

**Conflict of interest**

The authors have no conflict of interest to disclose.

**References**


