J Ped Surg Case Reports 1 (2013) 60–64

Contents lists available at SciVerse ScienceDirect

Journal of Pediatric Surgery CASE REPORTS

journal homepage: www.jpscasereports.com

# Association of duodenal and biliary atresias in Martinez–Frias Syndrome: A very rare case

Bircan Savran [a,*], Ahmet Kocak [b], Yasin Tugrul Karakus [c], Yasar Durmaz [c], Ayse Nur Deger [d]

[a] Department of Pediatric Surgery, Dumlupinar University Faculty of Medicine, Kutahya 43030, Turkey
[b] Department of Histology and Embryology, Dumlupinar University Faculty of Medicine, Kutahya 43030, Turkey
[c] Department of Pediatrics, Dumlupinar University Faculty of Medicine, Kutahya 43030, Turkey
[d] Department of Pathology, Dumlupinar University Faculty of Medicine, Kutahya 43030, Turkey

ARTICLE INFO

*Article history:*
Received 11 February 2013
Received in revised form 17 March 2013
Accepted 19 March 2013

*Key words:*
Martinez–Frias Syndrome
Duodenal atresia
Biliary atresia

ABSTRACT

Martinez–Frias Syndrome (MFS) is a very rarely seen condition with autosomal recessive inheritance and characterized by the presence of duodenal atresia, extrahepatic biliary atresia, hypoplastic pancreas, intrauterine growth retardation (IUGR) with or without tracheoesophageal fistula. To best of our knowledge, only six patients with MFS have been reported in the literature so far.



Martinez–Frias Syndrome (MFS), which is characterized by atresia and obliteration of duodenum and extrahepatic biliary duct, hypoplastic pancreas and intrauterine growth retardation (IUGR) with or without tracheoesophageal fistula, has been firstly described in 1992 by Martinez and Frias. MFS is a very rare condition with autosomal recessive inheritance [1]. Some other abnormalities such as esophageal atresia, rectoanal atresia, cardiac disorders and hipospadias can be observed in patients with MFS, but these findings may not be necessarily accompany with the disease [2–4]. The course of this syndrome is very serious, with the longest survival period of 10 months among the previously reported six cases [3].

## 1. Case report

A female neonatal infant weighing 2260 g was diagnosed as having antenatal duodenal atresia. A nasogastric (NG) tube was inserted to the baby immediately after delivery and approximately 40 ml of gastric content without bile was excreted from the NG tube. Because there was a “double-bubble” sign in direct radiography image, a second stomach-duodenum radiograph was taken following the administration of radio-opaque contrast fluid and no passage observed beyond duodenum. The patient who has been diagnosed as having duodenal atresia type-3 malformation was undergone surgical duodeno-duodenostomy intervention. During the surgical anastomosis operation, no bile excretion or residue was found in duodenum and pancreas was in hypoplastic appearance. Nutrition was initiated via oral way at 11th day following the operation. Acholic gaita defecation was observed during postoperative 12th day. Because of a superimposed jaundice condition and high direct plasma bilirubin levels rising up to 14 mg/dl during the follow-up controls, a concern came into the mind that there might be an extrahepatic biliary atresia possibility in our patient, but HIDA (hepatobiliary iminodiacetic acid) scintigraphy imaging could not be performed to reveal whether an atresia was present at this level. Instead, intraoperative cholangiography was achieved at postnatal 24th day (Fig. 1). Beside this, our patient has undergone Kasai portoenterostomy operation for biliary atresia type-1 treatment (Fig. 2).

Because an early cholangitis attack has occurred three weeks after the operation, high dose methylprednisolone (10 mg/kg) plus ursodeoxycholic acid (40 mg/kg) treatment was initiated. Fortunately, our patient was able to get over this serious condition and her weight was 2060 grams at postnatal 53rd day. During the first 6 months, she has been fed with a special infant formula called “Pregestimil” containing medium chain fatty acids (MCFA) combined with vitamins A, D, E, and K. Currently, she is 13 months old and her weight is 6700 g. The genetic analysis of the patient has indicated normal (46, XX) karyotype. Her parents are cousins and

* Corresponding author. Tel.: +90 274 265 20 31.
*E-mail address:* bircansavran@gmail.com (B. Savran).

2213-5766 
http://dx.doi.org/10.1016/j.epsc.2013.03.009

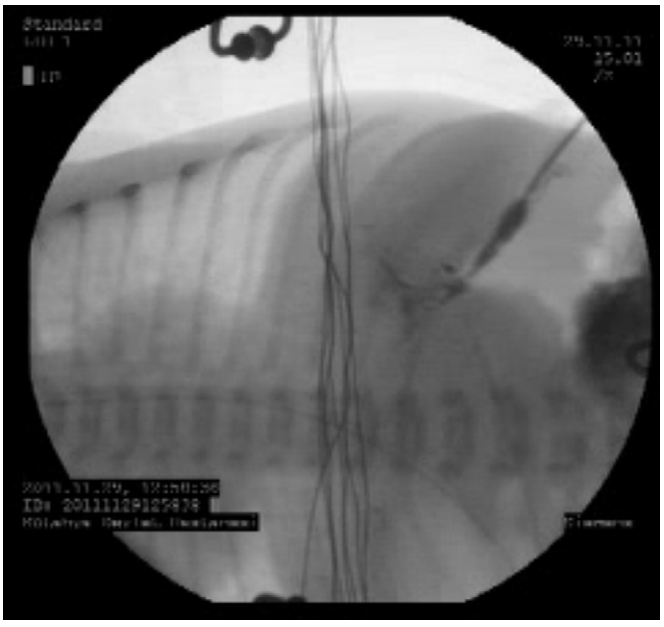

**Fig. 1.** Intraoperative cholangiography image. The gallbladder is in rudimentary appearance and atretic extrahepatic duct can also be observed. The opac fluid passes through the intrahepatic ducts but, there is no passage to the duodenum.

first-degree relatives. Our patient is the second child of the family and the genetical structure of her syndrome is in accordance with autosomal recessive inheritance.

## 2. Results

Our patient's condition was identical to MFS, which is characterized by the presence of the complicated combination of duodenal atresia, extrahepatic biliary atresia, hypoplastic pancreas, intrauterine growth retardation, and tracheoesophageal fistula [1]. MFS has been reported four times in the literature and the total number of reported cases is six so far, however none of these reported cases are alive today [1–4]. At this point, it may be favorable to take into consideration that our patient is the first and still living patient with MFS among the previously reported cases.

Ultrasonographic imaging of thyroid and urinary tract has exhibited normal anatomical structure with regular margins. Significant enlargement was observed in right cavities in transthoracic echocardiography. There was a 10 mm of defective site on interatrial septum, which was in compliance with secondary type atrial septal defect. A left-to-right passage flow was also observed in color Doppler ultrasonography imaging. The mean systolic pulmonary pressure was measured as 60 mm Hg. The excised gallbladder was in fibrotic appearance and its lumen was obliterated. In histopathological examination, no lumen was present in many sites of the sac. In mucosal areas with lumen, mixed inflammatory infiltration accompanied by reactive atypical findings was observed. The wall of gallbladder was in fibrotic appearance and no smooth muscle tissue was observed (Fig. 3). Histopathological findings of fibrosis, stenosis and inflammation were in compliance with biliary atresia.

## 3. Discussion

Duodenal atresia is closely associated with several conditions including extrahepatic biliary atresia, hypoplastic pancreas and intrauterine growth retardation (IUGR) with or without tracheoesophageal fistula in patients with MFS [1]. Some other congenital abnormalities such as esophageal atresia, rectoanal atresia, cardiac defects and hypospadias can also accompany with MFS, but these latter may not be necessarily seen in whole cases [2–4].

In a case report, Mitchell-Riley et al have described a new variant of the disease in which duodenal atresia, extrahepatic biliary atresia, pancreatic hypoplasia, and neonatal diabetes have been observed without tracheoesophageal fistula in 5 infants [5]. It was mentioned that both variants have a very critical prognosis. In the literature, 6 patients with MFS and 10 patients with Mitchell-Riley Syndrome have been reported, all of which died during 10 months of mean survival period except one. Beside this, Maegawa et al have described a new variant of mandibulofacial dysostosis syndrome, which exhibits similar characteristics to those of the MFS, but considered as a possible different entity [6].

In this syndrome, bilateral microtia with the absence of external auditory meati and Mondini dysplasia, left hemiaplasia of the thyroid and anterior displacement of the anus have also been reported along with duodenal atresia and intrahepatic/extrahepatic biliary atresia conditions. In our case, blood glucose level was in normal range and no sign of neonatal diabetes was present during follow-up visits. Our patient's status does not comply with Mitchell-Riley Syndrome. Furthermore, thyroidal USG (ultrasonography) has also indicated normal anatomical structure and her bilateral external acoustic meatus canals and auricles were normal. When previously reported MFS cases are evaluated, it is understood that the patient with longest survival duration died because of the complications of recurrent bronchiolitis attacks [3].

Our case has exposed to very frequent and serious bronchiolitis attacks until when she was 9 months old and also, she could not gain weight for a long time. In esophagogram imaging performed using digital opaque substance, no sign of tracheo/gastroesophageal fistula was observed in our patient. Beginning from the 9th

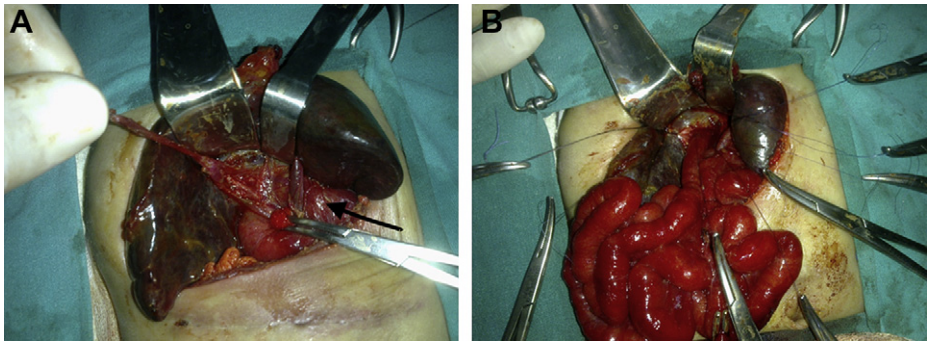


**Fig. 2.** (A): The intestinal segment (arrow) residual site form a previous duodenoduodenostomy operation is observed as preportal duodenal vein and cholestatic liver, during Kasai portoenterostomy operation at postnatal day 24. (B): The completion of portoenterostomy operation with Roux-en-Y method.

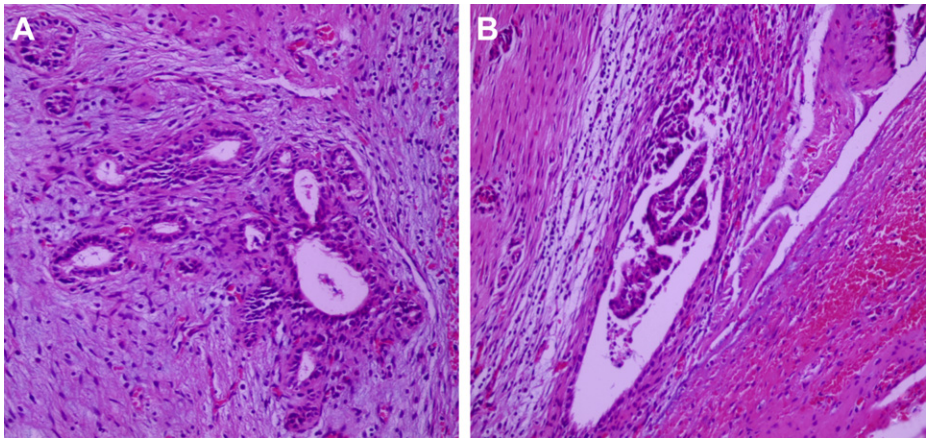


**Fig. 3.** (A): Fibrotic appearance of the gallbladder. (B): Diffuse infiltration sites and narrowed lumen in gallbladder mucosa.

month, she has regularly gained weight and has never had a bronchiolitis attack since then.

Duodenal atresia is attributed to a condition described with "failure of recanalization" concept. According to this theory, duodenal lumen opens again during 12th week of the fetal period after a temporary developmental obliteration. If a defect occurs during this process, this may lead to duodenal atresia [7]. The biliary canal is originated from the hepatic diverticulum during 4th week and becomes evident with all of its components in 5th week. Elongating biliary and pancreatic canals end in the closed cavity of duodenum in 7th week. Superior and inferior orifices are formed in both margins of the hepatopancreatic canal between 8th and 12th weeks and connects with each other, which thereby turn this canal to an opened tube [8]. Galan-Gomez et al have suggested that a possible blastogenetic abnormality, which interferes with the connection and merging of duodenal, pancreatic and biliary canals at the middle line axis, could lead to obliteration and atresia of the extrahepatic bile duct, which may accompany with duodenal atresia [4].

However, the association of duodenal atresia with the embryonic abnormalities of the biliary tract is very rare, with only a few cases reported in the literature [9]. In a study conducted on MFS by Gentile et al in 1999, it has been reported that there has been an increased expression activity in 6q21-q22 chromosomal region of the RFX-6 gene [3]. Another supporting evidence, which may confirm these latter findings came from Smith et al, who have mentioned that the vast majority of the Langerhans islet cell mass of the pancreatic tissue except those producing pancreatic polypeptides could not exhibit a normal course of development in knock-out mice lacking RFX-6 gene. These authors have also emphasized that some mutational changes were determined in RFX-6 gene regions of the infants with similar syndrome associated with neonatal diabetes condition via using genetic mapping method, which in turn may provide more information about the place and importance of the RFX-6 gene functioning in manipulation of the factors coordinating the pancreatic islet development in both mice and humans [10].

In a distinct study mainly focused on KCNJ11 gene, which is claimed to be related with the occurrence of diabetes along with other genes including ABCC8, GCK, IPF1, HNF1 beta, NeuroD1, and TCF7L2, no mutational change has been reported [11]. In the same study, it has also been found that there was no mutational change in HNF6, a new candidate gene to be studied for the investigation of the developmental features of liver, biliary tract, and pancreas. It is estimated that different and more comprehensive studies focusing on the syndrome in gene structure level would be carried out and thereby more information would be gathered on molecular level by the increased number of cases in the literature in the future.

## 4. Conclusion

All of the cases, which have been reported as having MFS died in a short time period. The most important aspect of our case is that she is the first patient who is still alive among the reported cases so far. For this reason, her condition can contribute to the current knowledge base about the course of MFS. Beside this, more comprehensive investigations are required in embryonic field to reveal the possible underlying mechanisms associated with duodenal and biliary abnormalities, as this kind of association is a very rare occasion.

### Conflict of interests

The authors declare that they have no relevant financial interests.

### Sources of funding

No additional or third party funding resource has been established and charged for this paper. Whole devices and tools used for surgical intervention and for other imaging or diagnostic assay method(s) belong to the property of our institution and research hospital.

### Acknowledgments

We hereby acknowledge dear Dr. Taner Sen and Dr. Emre Tepeli for their precious contributions to this research during the study process.

### References

[1] Martinez-Frias ML, Frias JL, Galan E, Domingo R, Paisán L, Blanco M. Tracheoesophageal fistula, gastrointestinal abnormalities, hypospadias, and prenatal growth deficiency. Am J Med Genet 1992;44:352–5.
[2] Anneren G, Meurling S, Lilja H, Wallander J, von Dobeln U. Lethal autosomal recessive syndrome with intrauterine growth retardation, intra- and extrahepatic biliary atresia, and esophageal and duodenal atresia. Am J Med Genet 1998;78:306–7.
[3] Gentile M, Fiorente P. Esophageal, duodenal, rectoanal and biliary atresia, intestinal malrotation, malformed/hypoplastic pancreas, and hypospadias: further evidence of a new distinct syndrome. Am J Med Genet 1999;87:82–3.
[4] Galan-Gomez E, Sanchez EB, Arias-Castro S, Cardesa-García JJ. Intrauterine growth retardation, duodenal and extrahepatic biliary atresia, hypoplastic pancreas and other intestinal anomalies: further evidence of the Martínez-Frías syndrome. Eur J Med Genet 2007;50:144–8.

[5] Mitchell J, Punthakee Z, Lo B, Bernard C, Chong K, Newman C, et al. Neonatal diabetes, with hypoplastic pancreas, intestinal atresia and gall bladder hypoplasia: search for the aetiology of a new autosomal recessive syndrome. Diabetologia 2004;47:2160–7.
[6] Chitayat D, Blaser S, Whyte H, Whyte H, Thomas M, Kim P, et al. Duodenal and biliary atresia associated with facial, thyroid and auditory apparatus abnormalities: a new mandibulofacial dysostosis syndrome? Clin Dysmorphol 2006; 15:191–6.
[7] Lee SE, Kim HY, Jung SE, Lee SC, Park KW, Kim WK, et al. Situs anomalies and gastrointestinal abnormalities. J Pediatr Surg 2006;41:1237–42.
[8] Ando H. Embryology of the biliary tract. Dig Surg 2010;27:87–9.
[9] Knechtle SJ, Filston HC. Anomalous biliary ducts associated with duodenal atresia. J Pediatr Surg 1990;25:1266–9.
[10] Smith SB, Qu HQ, Taleb NK, Kishimoto NY, Scheel DW, Lu Y, et al. Rfx6 directs islet formation and insulin production in mice and humans. Nature 2010;463: 775–80.
[11] Chappell L, Gorman S, Campbell F, Ellard S, Rice G, Dobbie A, et al. A further example of a distinctive autosomal recessive syndrome comprising neonatal diabetes mellitus, intestinal atresias and gall bladder agenesis. Am J Med Genet 2008;146A:1713–7.

## Summary of the literature reviews

[1] Martinez-Frias ML, Frias JL, Galan E, Domingo R, Paisán L, Blanco M. Tracheoesophageal fistula, gastrointestinal abnormalities, hypospadias, and prenatal growth deficiency. Am J Med Genet 1992;44:352–5.

**Abstract**

We studied 2 sibs, born to consanguineous parents, who presented with an MCA pattern, which includes low birth weight, tracheo-esophageal fistula, duodenal atresia, extrahepatic biliary atresia, hypoplastic pancreas, and hypospadias. This constellation of congenital anomalies appears to be a previously unreported autosomal recessive syndrome. A computerized search of the data files of the Spanish Collaborative Study of Congenital Malformations (ECEMC) identified 3 other unrelated infants with intestinal atresias, hypospadias, and low birth weight. These cases may represent a milder expression of the same syndrome.

[2] Anneren G, Meurling S, Lilja H, Wallander J, von Döbeln U. Lethal autosomal recessive syndrome with intrauterine growth retardation, intra- and extrahepatic biliary atresia, and esophageal and duodenal atresia. Am J Med Genet 1998;78:306–7.

**Abstract**

We describe 2 sibs, a boy and a girl, with a multiple congenital anomalies (MCA) syndrome, born to healthy, consanguineous parents. The syndrome comprises low birth weight, malrotation, duodenal and esophageal atresia, intra and extrahepatic biliary atresia, and hypoplastic pancreas. Both children died during infancy. In 1992 Martinez-Frias et al described 2 sibs with an MCA pattern including low birth weight and biliary, duodenal, and esophageal malformation, and postulated it to be a new autosomal recessive syndromffecting the midline. The two children described below showed many similarities to that syndrome, but had some anomalies not previously observed. We compare the present cases with the previous ones and discuss whether our cases represent a variant form of the syndrome described by Martinez-Frias et al [1992].

[3] Gentile M, Fiorente P. Esophageal, duodenal, rectoanal and biliary atresia, intestinal malrotation, malformed/hypoplastic pancreas, and hypospadias: further evidence of a new distinct syndrome. Am J Med Genet 1999;87:82–3.

**Abstract**

Two sibs from consanguineous parents with a lethal syndrome characterized by low birthweight, tracheoesophageal fistula, duodenal and extrahepatic biliary atresia, hypoplastic pancreas, and hypospadias were described by Martinez-Frias et al [1992]. In the same study, three further patients with a similar but milder phenotype were identified, confirming the hypothesis of a new autosomal recessive syndrome with midline defects and variable expressivity. Recently Anneren et al [1998], two other sibs born to consanguineous parents were reported and probably represent a variant of the same syndrome. Here we report on a patient with an MCA pattern strictly similar to that observed in the patients mentioned above.

[4] Galan-Gomez E, Sanchez EB, Arias-Castro S, Cardesa-García JJ. Intrauterine growth retardation, duodenal and extrahepatic biliary atresia, hypoplastic pancreas and other intestinal anomalies: further evidence of the Martínez-Frías syndrome. Eur J Med Genet 2007;50:144–8.

**Abstract**

We describe a patient born to consanguineous parents, who presented with an MCA pattern characterized by low birth weight, duodenal atresia, extrahepatic biliary atresia, hypoplastic pancreas and intestinal malrotation. The infant died 60 days after birth. Chromosomes at 550–600 band levels were normal for a female (46, XX). This patient confirmed the autosomal recessive disorder previously described by our group. The pathogenesis of this syndrome is most probably of blastogenetic origin mainly affecting midline developmental duodenal biliary pancreatic junction.

[5] Mitchell J, Punthakee Z, Lo B, Bernard C, Chong K, Newman C, et al. Neonatal diabetes, with hypoplastic pancreas, intestinal atresia and gall bladder hypoplasia: search for the etiology of a new autosomal recessive syndrome. Diabetologia 2004;47:2160–7.

**Abstract**

**Aims/hypothesis**

Neonatal diabetes is a rare disease with several identified molecular aetiologies. Despite associations with other malformations, neonatal diabetes with intestinal and biliary anomalies has not been described. The current study aims to describe a new syndrome, and to examine a possible link with one of three genes known to cause neonatal diabetes.

**Methods**

Five clinical cases are described. Immunohistochemical staining for pancreatic islet hormones was performed on three of the infants. DNA from one infant was analyzed for abnormalities of the *PLAGL-1* (*ZAC*), glucokinase and *PDX-1* (*IPF-1*) genes.

**Results**

Five infants (two sibling pairs from two families, and an isolated case) presented with neonatal diabetes, hypoplastic or annular pancreas, jejunal atresia, duodenal atresia and gall bladder aplasia or hypoplasia. One sibling pair was born to consanguineous parents. One patient with a milder form is surviving free of insulin. Four children died in the first year of life despite aggressive medical management. Pancreatic immunohistochemistry revealed few scattered chromogranin-A-positive cell clusters but complete absence of insulin, glucagon and somatostatin. Exocrine histology was variable. In one case from the consanguineous family, molecular analysis showed no duplication or uniparental isodisomy of *PLAGL-1* at 6q24, no contiguous gene deletion involving the glucokinase gene, and no mutation in the coding sequences or splice sites of *PDX-1*.

**Conclusions/interpretation**

This combination of multiple congenital abnormalities has not been previously described and probably represents a new autosomal recessive syndrome involving a genetic abnormality that interferes with normal islet development and whose aetiology is as yet unknown.

[6] Maegawa GH, Chitayat D, Blaser S, Whyte H, Thomas M, Kim P, et al. Duodenal and biliary atresia associated with facial, thyroid and auditory apparatus abnormalities: a new mandibulofacial dysostosis syndrome? Clin Dysmorphol 2006;15:191–6.

**Abstract**

We report a female child born at 36 weeks of gestation with multiple abnormalities including dysmorphic and coarse facial features with features of mandibulofacial dysostosis that include bilateral microtia with the absence of external auditory meati and Mondini dysplasia as well as, duodenal atresia, intestinal malrotation, anterior displacement of the anus, left hemiaplasia of the thyroid and biliary atresia in sibs. The associations of duodenal atresia with intrahepatic and extrahepatic biliary atresia in sibs have been reported, suggesting an autosomal recessive syndrome. However, the associated external, middle and internal ear anomalies and the thyroid malformation, however, have not been reported in this condition. To the best of our knowledge, this is a hitherto new syndrome with an unknown inheritance.

[7] Lee SE, Kim HY, Jung SE, Lee SC, Park KW, Kim WK, et al. Situs anomalies and gastrointestinal abnormalities. J Pediatr Surg 2006;41:1237–42.

**Abstract**

**Background/purpose**

The aim of the study was to review the gastrointestinal abnormalities occurring in association with situs anomalies.

**Methods**

Patients with situs anomalies were identified from the medical records of pediatric patients of Seoul National University Children's Hospital from January 1980 to July 2004. Retrospective study was undertaken. Diagnosis was made on the basis of the information obtained from a combination of echocardiography, angiography, abdominal ultrasonography, liver scan, upper gastrointestinal study, or abdominal computed tomography.

**Results**

A total 67 patients diagnosed as having situs anomalies were identified. There were 40 males and 26 females (1.54:1). Of these 67 patients, 45 patients (67%) were diagnosed as having situs inversus, 16 patients (24%) as having right isomerism, and 6 patients (9%) as having left isomerism. Of 45 patients with situs inversus, there were 26 patients (58%) who had intraabdominal abnormalities. These were duodenal atresia, biliary atresia, gastroschisis with malrotation, congenital hepatic fibrosis, tracheoesophageal fistula (type C), Currarino's triad, and pheochromocytoma. Of 16 patients with right isomerism, there were 14 patients (88%) who had intraabdominal abnormalities. These were hiatal hernia and diaphragmatic hernia. Of 6 patients with left isomerism, there were 4 patients (67%) who had intraabdominal abnormalities. These were malrotation and biliary atresia.

**Conclusion**

When a patient is noted to have congenital heart disease as part of situs anomalies, or if an atypical position of organs is noted at imaging evaluation, we recommend that the patient undergo chest radiography, abdominal ultrasonography, upper gastrointestinal study, and abdominal computed tomography.

[8] Ando H. Embryology of the biliary tract. Dig Surg 2010;27:87–9.

**Abstract**

A hepatic diverticulum appears in the ventral wall of the primitive midgut early in the 4th week of intrauterine life in the development of the human embryo. This small diverticulum is the anlage for the development of the liver, extrahepatic biliary ducts, gallbladder, and ventral pancreas. By the 5th week, all elements of the biliary tree are recognizable. Marked elongation of the common duct occurs with plugging of the lumen by epithelial cells. Recanalization of the lumen of the common duct starts at the end of the 5th week and moves slowly distally. By the 6th week, the common duct and ventral pancreatic bud rotate 180 degrees clockwise around the duodenum. Early in the 7th week, the bile and pancreatic ducts end in closed cavities of the duodenum. Between the early 8th and 12th week, hepatopancreatic ducts have both superior and inferior orifices. Of these two orifices, the inferior one is usually suppressed. The muscle of the sphincter of Oddi develops from a concentric ring of mesenchyme surrounding the preampullary portion of the bile and pancreatic ducts. At about the 10th week, the muscle of the sphincter of Oddi undergoes differentiation. In the 16th week, the muscularis propria extends from just outside the fenestra to the upper end of the ampulla. By the 28th week, the musculus proprius is differentiated almost to the distal end of the ampulla.

[9] Knechtle SJ, Filston HC. Anomalous biliary ducts associated with duodenal atresia. J Pediatr Surg 1990;25:1266–9.

**Abstract**

Duodenal atresia is rarely associated with anomalous biliary ducts that permit communication between the proximal and distal duodenal segments. Two such cases are presented herein and the literature is reviewed. Although the typical radiographic pattern of duodenal atresia is the "double bubble" sign with absence of distal bowel gas, air may be present in the distal bowel when anomalous bile ducts provide a conduit around the atretic segment. Contrast studies are generally not performed in the typical clinical and radiographic evaluation of duodenal atresia; however, an upper gastrointestinal series may be useful in defining the more complex anomaly. Clinical presentation may occur relatively late if the biliary communication is large enough to permit passage of some milk or formula. Care should be taken at surgery to avoid obstruction or injury to the anomalous bile ducts, and operative cholangiography may be useful to document continued bile duct patency following repair of the atresia. Theories of the etiology of this anomaly relate to interference with recanalization of the duodenum by the process of hepatopancreatic duct formation and persistence of the primitive "dual duct" stage.

[10] Smith SB, Qu HQ, Taleb NK, Kishimoto NY, Scheel DW, Lu Y, et al. Rfx6 directs islet formation and insulin production in mice and humans. Nature 2010;463:775–80.

**Abstract**

Insulin from the beta-cells of the pancreatic islets of Langerhans controls energy homeostasis in vertebrates, and its deficiency causes Diabetes mellitus. During embryonic development, the transcription factor neurogenin 3 (Neurog3) initiates the differentiation of the beta-cells and other islet cell types from pancreatic endoderm, but the genetic program that subsequently completes this differentiation remains incompletely understood. Here we show that the transcription factor Rfx6 directs islet cell differentiation downstream of Neurog3. Mice lacking Rfx6 failed to generate any of the normal islet cell types except for pancreatic-polypeptide producing cells. In human infants with a similar autosomal recessive syndrome of neonatal diabetes, genetic mapping and subsequent sequencing identified mutations in the human RFX6 gene. These studies demonstrate a unique position for Rfx6 in the hierarchy of factors that coordinate pancreatic islet development in both mice and humans. Rfx6 could prove useful in efforts to generate beta-cells for patients with diabetes.

[11] Chappell L, Gorman S, Campbell F, Ellard S, Rice G, Dobbie A, et al. A further example of a distinctive autosomal recessive syndrome comprising neonatal diabetes mellitus, intestinal atresias and gallbladder agenesis. Am J Med Genet 2008;146A:1713–7.

**Abstract**

We report a patient born to consanguineous parents as a further example of a recently described phenotype comprising neonatal diabetes, intestinal atresias, and gall bladder agenesis. Other reports have described cases with overlapping patterns including malrotation, biliary atresia and pancreatic hypoplasia (e.g., as described by Martínez-Frías). We propose that these cases may represent variations of the same syndrome. It is likely that this disorder is inherited as an autosomal recessive trait. Our case is the first to have neonatal diabetes without a demonstrable structural pancreatic abnormality, showing that a deficit in pancreatic function is involved. We sequenced genes with a recognized role in monogenic forms of diabetes, including KCNJ11, ABCC8, GCK, IPF1, HNF1beta, NeuroD1, and TCF7L2, as well as a novel candidate gene, HNF6, known to be involved in hepatobiliary and pancreatic development, but did not identify mutations.