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Severe Combined Immunodeficiency Syndrome Associated With Autosomal Recessive Familial Multiple Gastrointestinal Atresias: Study of a Family

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Hereditary multiple atresias involving the gastrointestinal tract from pylorus to rectum are the most unusual form of intestinal atresia; the type of inheritance was suggested to be autosomal recessive. The inheritance of the severe combined immunodeficiency syndrome can be autosomal recessive or X-linked.

We report on 3 sibs with multiple-level intestinal atresias. One sib had severe combined immunodeficiency syndrome and clinical histories of the other 2 sibs strongly suggested a congenital immunodeficiency syndrome. The parents of those children were healthy and nonconsanguineous.

To our knowledge, this is the first report of the association of multiple gastrointestinal atresias and immunodeficiency which appears to have an autosomal recessive pattern of transmission. Our family report suggests that, in the presence of multiple gastrointestinal atresias, attention should be given to possible associated immunological disorders.

KEY WORDS: autosomal recessive inheritance, X-linked inheritance, genetic counseling

INTRODUCTION

Intestinal atresia is one of the common causes of intestinal obstruction in the neonatal period. Various types of gastrointestinal atresia have been described: pyloric, duodenal, jejunal (apple peel syndrome), colonic, and multiple. The latter seems to be different from the other types [Martin et al., 1976]. Familial occurrence of multiple gastrointestinal atresias has been reported in 8 families [Mishalany and Der Kaloustian, 1971; Guttman et al., 1973; Martin et al., 1976; Arnal-Monreal et al., 1983; Puri et al., 1985; Blake and Puri, 1986], and the type of inheritance was suggested to be autosomal recessive (McKusick MIM No. 24315).

Severe combined immunodeficiency (SCID) is a syndrome characterized by important defects in T and B lymphocyte function. While the majority are isolated cases, both autosomal recessive and X-linked inheritance have been described [Buckley, 1987].

We report on 3 sibs with multiple-level intestinal atresias. One sib had SCID and clinical histories of the other 2 sibs strongly suggested a congenital immunodeficiency syndrome.

CLINICAL REPORTS

Family History

Both parents were healthy and unrelated and came from the same region in France. The first child, a boy, is age 10 years, and well, with no demonstrable anomalies. The second child, a girl, was stillborn; post-mortem examination was not performed. The fourth child, a girl, is age 5 years, and well (Fig. 1).

Patient 1

A boy was the third child of the family. He was born at 37 weeks gestation. The pregnancy was complicated by hydramnios. Birthweight was 2,130 g. Immediately after birth he developed abdominal distension. An abdominal radiograph demonstrated air within a dilated stomach and no air beyond the antral region. At laparotomy a diaphragm was found in the prepyloric region, and another one in the ileo-caecal region. The pyloric diaphragm was excised and a pyloroplasty performed; the ileo-caecal diaphragm was perforated with a probe and a colostomy was performed. Nutrition was maintained in-

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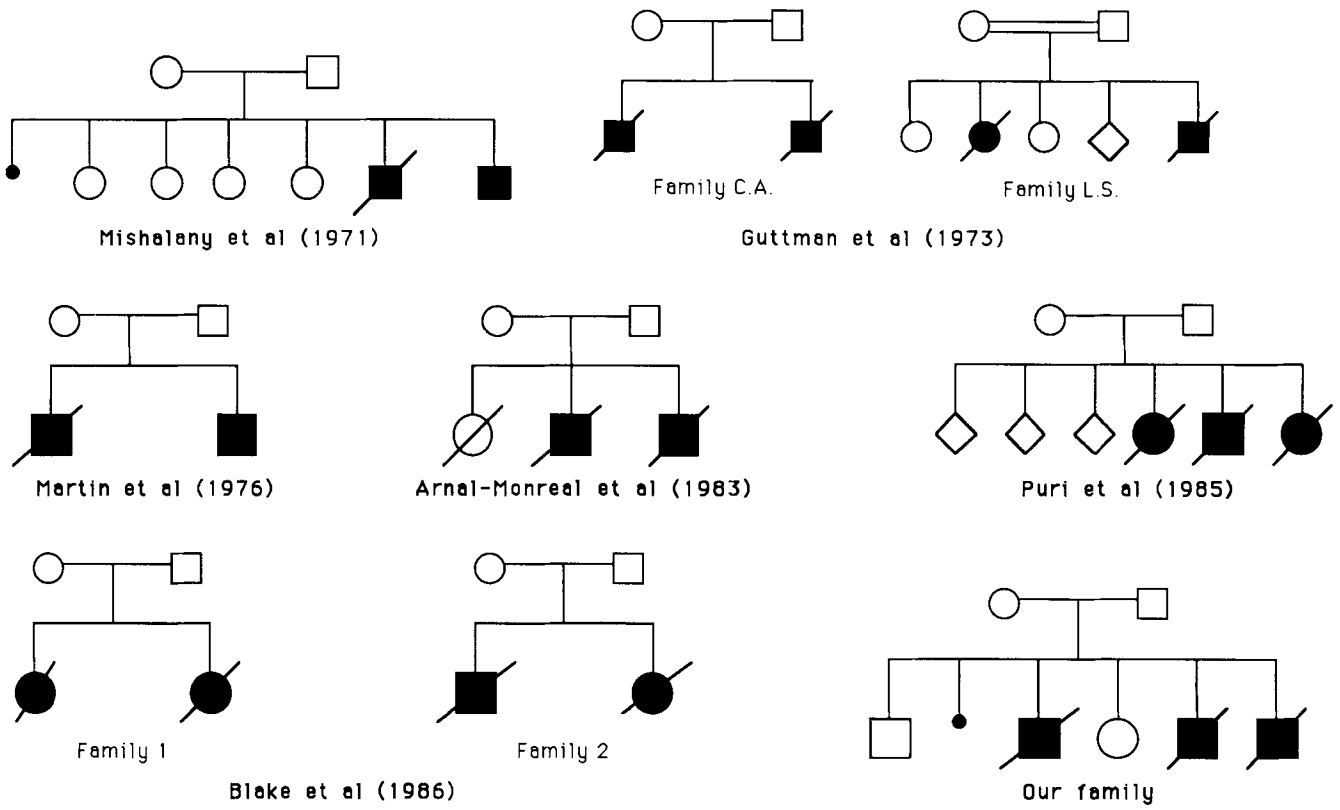

Fig. 1. Eight families in which familial occurrence of multiple gastrointestinal atresias has been reported.

travenously. At a second laparotomy, a caecal duplication was discovered. The child died from *Streptococcus foecalis* septicemia at age 56 days. The only immunological data available was an absolute lymphocyte count which was between 600 and 900/mm^3 before the septicemia occurred. R-banded chromosomes were normal.

Patient 2

The brother of patient 1 was the fifth child of the family. He was born at 37 weeks gestation; during pregnancy an intestinal obstructive process was suspected by ultrasound examination. Birthweight was 2,500 g. A plain radiograph taken soon after birth showed gas in the stomach but not air in the intestine. At laparotomy a diaphragm was found in the prepyloric region which was excised and a pyloroplasty was performed; there were also an ileal atresia, a colonic atresia, and a rectosigmoidal atresia. An ileostomy and a colostomy were performed. On the 17th postoperative day, reexploration was carried out for recurring obstruction which occurred at several levels of the intestine, beginning with the antral diaphragm, which was now more widely resected. Postoperatively, the child was placed on total parenteral nutrition. At age 1½ months the infant developed *Pseudomonas* septicemia. He died at age 3½ months with graft vs. host reaction (GVHR), i.e., skin and liver localization both assessed by a biopsy, 15 days after a blood transfusion. The only immunological data available were gamma globulin levels which decreased to 2.0 g/l, and the absolute lymphocyte count, which was 360/mm^3 before the occurrence of septicemia. G-banded chromosomes were normal.

Patient 3

The brother of patients 1 and 2 was the sixth child of the family. The pregnancy lasted 38 weeks and was complicated by hydramnios; ultrasound examination at 25 weeks gestation showed a dilatation of the small bowel. Birthweight was 2,830 g. An abdominal radiograph was taken soon after birth, which showed a dilated stomach and no gas beyond the antral region. At laparotomy, a diaphragm was present in the prepyloric region which was excised and a pyloroplasty carried out; the distal small bowel was atretic and a double ileostomy was performed; there was also a caecal diaphragm which was resected and an end to end ileo-colonic anastomosis was carried out. The infant received total parenteral nutrition. When necessary, blood transfusions were given by using irradiated and cytomegalovirus negative blood in order to avoid GVHR. Despite postoperative therapy by cisapride (maximal dose: 3 mg/kg/day), peristalsis was never achieved and the child died at the age of 7 months. Immunologic evaluation showed decreased levels of serum immunoglobulins: IgG < 0.42 g/l, IgA < 0.07 g/l, IgM < 0.20 g/l, IgE $= 18$ UI/ml. Delayed hypersensitivity skin tests were nonreactive. Absolute lymphocyte counts were between 400 and 1,100/mm^3. There was no formation of erythrocyte ro-

settes. Lymphocyte subset studied by immunofluorescence revealed depressed percentages of T_3 (<1%), T_4 (<1%), and T_8 (0%) cells, and normal proportion of B lymphocytes (IgM-bearing cells = 11%). Proliferative reponses to phytohemagglutinin were totally abolished. Adenosine deaminase activity was not decreased. G-banded chromosomes were normal.

DISCUSSION

Hereditary multiple atresias involving the gastrointestinal tract from pylorus to rectum are the most unusual form of intestinal atresia. The aetiology of this syndrome is not clear: some authors think that atresias are a consequence of an intrauterine inflammatory process [Teja et al., 1981] or of multiple intrauterine vascular accidents [Collins et al., 1986]. Arnal-Monreal et al. [1983] and Puri and Fujimoto [1988] suggested that these multiple atresias may be the consequence of a malformation of the gastrointestinal tract occurring during early fetal life. Familial occurrence of multiple gastrointestinal atresias has been reported in 8 families, in which the type of inheritance was suggested to be autosomal recessive [Mishalany and Der Kaloustian, 1971; Guttman et al., 1973; Martin et al., 1976; Arnal-Monreal et al., 1983; Puri et al., 1985; Blake and Puri, 1986] (Fig. 1). It can be speculated that at a certain stage of development, a genetically determined "factor" would act to induce the transition from the solid stage to the final hollow stage. In patients with the syndrome, an autosomal recessively inherited mutant gene, altering the nature of this "factor," may be responsible for the persistence of the diaphragms.

In the studied family, extensive immunological investigations could be performed only in the third sib: the data pointed to a combined defect of T-cells (low number of circulating T-cells, nonreactive delayed hypersensitivity skin tests) and of B-cells (immunoglobulin deficiency). In the second sib gamma globulin levels and absolute lymphocyte count were decreased, and he died with a GVHR. These data strongly suggested an SCID because in addition to their undue susceptibility to infection, these infants also lack the ability to reject foreign tissue and are, therefore, at risk for GVHR [Buckley, 1987]. In the first sib the only immunological data documented consisted of lymphopenia, and he died of septicemia. In the other reports of families with multiple gastrointestinal atresias, immunologic data have not been described. Analysis of those reports and of other isolated cases of multiple gastrointestinal atresias [Chittmittrapap, 1988] allow us to think that some of the patients also could have immunodeficiency because of the high incidence of infections observed.

In approximately 40% of the patients with the autosomal recessive form of SCID, an absence of the enzyme adenosine deaminase has been observed. In our family adenosine deaminase activity was normal and rib-cage abnormalities which are, in some patients, distinguishing features of this deficiency, were not present.

Many diseases of the gastrointestinal tract such as gluten-induced enteropathy, jejunal abnormalities, and intestinal lymphangiectasia can lead to secondary immunodeficiency [Fawcett et al., 1986]. In our patients, we think that SCID was a primary defect because the nutritional status was not altered, the infections occurred early in life, and the clinical and biological findings were quite severe.

To our knowledge, this is the first report of a family in which 3 sibs had multiple gastrointestinal atresias and immunodeficiency. Since the chromosomes of the 3 children were normal, this association is not due to a demonstrable chromosomal anomaly. The inheritance for this association could be autosomal recessive or X-linked. However, we think that this condition has an autosomal recessive pattern of transmission, because the type of inheritance of multiple gastrointestinal atresias (autosomal recessive) is considered to be quite certain. It is possible that the 2 genes which express the 2 conditions are closely linked. The alternative explanation is that a single autosomal recessive or X-linked recessive mutation is responsible for a new syndrome affecting the gastrointestinal and the immune systems. The development and/or function of both systems may be co-regulated by the same gene products.

Prenatal diagnosis of multiple gastrointestinal atresias is possible by ultrasound examination from 21 weeks' gestation [Skoll et al., 1987]. Prenatal diagnosis of SCID is based on the enumeration of lymphoid cells, total T lymphocytes, T lymphocyte subsets, and B lymphocytes present in a microsample of pure fetal blood obtained at fetoscopy performed during the mid-to-late second trimester (18–22 weeks gestation) [Linch and Levinsky, 1983]. As a measure of T lymphocyte function, the proliferative response of fetal lymphocytes to the T lymphocyte mitogen phytohemagglutinin has also been used as an additional piece of confirmatory information [Durandy and Griscelli, 1983].

The present report suggests that in the presence of multiple gastrointestinal atresias, attention should be directed to possible associated immunological disorders which can indicate the need of prenatal diagnosis in the future pregnancies.

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