

Gastroesophageal reflux and severe combined immunodeficiency

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Background: Gastrointestinal and respiratory symptoms and failure to thrive not associated with infections or medications were noted in patients with severe combined immunodeficiency. **Objective:** The aim of our study was to determine the frequency of gastroesophageal reflux in patients with severe combined immunodeficiency.

Methods: We studied the case histories of 73 pediatric patients who had been treated at Duke University Medical Center for severe combined immunodeficiency between 1982 and 1995. Charts were reviewed for documentation of gastroesophageal reflux on the basis of clinical course and results of barium swallow, esophageal pH probe monitoring, or endoscopy. To compare the incidence of gastroesophageal reflux in patients with severe combined immunodeficiency to known high-risk populations, we additionally tabulated the underlying diagnoses in an age-matched group of patients who underwent Nissen fundoplication from 1990 to 1995.

Results: We found clinically significant gastroesophageal reflux in 15 of the 73 patients (20.5%), much higher than has been reported in the normal population (0.1% to 0.3%, $p < 0.001$). Of patients treated between 1990 and the present, 10 of 36 (27.7%) had significant gastroesophageal reflux compared with five of 37 patients (13.5%) in the previous years. Thus with greater recognition and improved methods for diagnosis, the observed incidence of gastroesophageal reflux has increased greatly. The clinical presentations were not different from those of patients with other well-documented underlying diagnoses. Seven of the 15 patients (46.6%) did not respond to medical treatment with antacids, H_2 -blockers, and prokinetic agents and underwent surgical treatment. Indications for surgery included persistent esophagitis, vomiting, pneumonia, and growth failure. **Conclusions:** The reason for the high incidence of gastroesophageal reflux in patients with severe T-cell disorders remains unclear. Considering the frequency of this association, early recognition and treatment is important to enable adequate nutrition and prevent damage to the esophagus and lungs. (J Allergy Clin Immunol 1997;99:420-4.)

Key words: Gastroesophageal reflux, severe combined immunodeficiency, Nissen fundoplication

Severe combined immunodeficiency (SCID) is an inherited disorder with impaired function of both the

Abbreviations used

GER: Gastroesophageal reflux

SCID: Severe combined immune deficiency

cellular and humoral immune systems.^{1,2} Patients with this disease have severe, recurrent, often life-threatening infections that become clinically manifest in early infancy, after they have lost protection by maternal antibodies.³ Although antimicrobial therapy is necessary to treat acute infections and may be life-saving, prolonged survival requires reconstitution of the immune system by bone marrow transplantation, sometimes preceded by myeloablation.⁴ Gastrointestinal symptoms such as vomiting, diarrhea, or malabsorption are usually attributed to either infections or medications, but in many children gastrointestinal symptoms could not be explained by these common causes. Additionally, some of the children had respiratory problems not caused by infectious pathogens.

During the evaluation of these patients for the cause of their symptoms, we noted that there appeared to be a much higher incidence of gastroesophageal reflux (GER) in patients with SCID compared with the normal population. GER is a common condition in infancy characterized by repetitive regurgitation of gastric content into the esophagus. Although many infants have minor degrees of reflux, about 1 in 300 to 1 in 1000 have significant reflux and associated complications.⁵ Decreased tone in the lower esophageal sphincter, anatomic changes in the esophagus, increased gastric acidity, and poor esophageal clearance are some of the pathophysiologic factors leading to esophageal damage.⁶ Relief of symptoms after fundoplication in refractory asthma points to a close correlation between GER and bronchoconstrictive diseases.^{7,8} Additionally, an increased incidence of GER has recently been reported in patients allergic to cow's milk.⁹ It is also evident that patients with acquired, secondary immunodeficiencies are another high-risk GER population because of opportunistic infections.^{10,11} To determine a possible characteristic pattern of GER-associated symptoms in our patients, which may help to differentiate patients with SCID from patients with other underlying major defects, three main features were compared: respiratory problems, gastrointestinal symptoms, and failure to thrive including poor feeding. Many of the patients improved with medical management of their GER, but many

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others required surgical correction to control their symptoms. Our data make clear that careful monitoring and management of symptoms not related to infections or medications is necessary to improve the clinical course of patients with SCID.

METHODS

We studied the case histories of all patients with SCID who were followed up by the Duke Division of Pediatric Immunology and were seen between 1982 and 1995 ($n = 73$). Charts were reviewed for documentation of vomiting, malabsorption, feeding problems, failure to thrive, and respiratory symptoms-in particular, aspiration pneumonia. GER was considered on the basis of the clinical course and results of barium swallow, if aspiration was observed, but otherwise confirmed by results of esophageal pH probe monitoring or endoscopy. Three patients underwent lung biopsy, and seven underwent endoscopy and biopsy. Histologic findings in the esophagus revealed nonspecific inflammation, similar to that seen in patients without immune deficiency. Because of their age, no patients had studies of esophageal motility. Nearly all patients were treated with antacids, prokinetic agents, and H_2 antihistamines in the hospital during their treatment for immune deficiency. Patients received supplemental parenteral nutrition if oral intake was determined to be inadequate.

Patients with evidence of severe *Candida* infection of the esophagus, as well as patients with infectious or medication-associated pneumonia, were excluded from analysis. However, patients with well-documented aspiration pneumonia were included. Because of a perceived increase in the incidence of GER in the past 5 years, the study period was also analyzed separately from 1982 to 1989 and from 1990 to 1995.

The overall incidence of GER in pediatric patients at Duke is not known. Therefore to compare the incidence of reflux in patients with SCID with that of known high-risk populations, we tabulated the underlying diagnoses in an age-matched group of patients who underwent Nissen fundoplication from 1990 to 1995. Data were obtained from the Pediatric Surgery database and included all patients who either did not respond to medical treatment or for whom a trial of medications was not considered appropriate ($n = 121$). These included patients with a variety of anatomic abnormalities (diaphragmatic and paraesophageal hernia, tracheoesophageal fistula, esophageal stricture and atresia, pyloric stenosis), functional abnormalities (esophageal dysmotility, dyskinesia, and myopathy), congenital disorders other than immune deficiency (congenital heart disease, inborn errors of metabolism, Down syndrome, and other chromosomal abnormalities, hydrocephalus, severe intracranial abnormalities), immaturity (preterm infants, intrauterine infections, parental drug abuse), infantile cerebral palsy class II to III, and cystic fibrosis. Children who were otherwise considered to be normal were also included.

RESULTS

As shown in Table I, we found a significantly increased incidence of GER in patients with SCID (20.5%), compared with that reported in the normal population (0.3% to 0.1%, $p < 0.001$).⁵ The mean age at diagnosis of GER was 16.6 months (range, 3 months to 5 years). In most patients the symptoms of respiratory distress and failure to thrive led to an initial diagnosis of SCID, and GER was suspected and diagnosed after referral. However, since these pa-

TABLE I. Incidence of GER in patients with SCID

	Observation period		
	Total period 1982-95	1982-89	1990-95
No. Patients with SCID	73	37	36
No. with GER	15 (21%)	5 (14%)	10 (28%)
No. undergoing surgery	7 (40%)	1 (20%)	6 (50%)

tients were referred because of their immune deficiency, this may not reflect the relative importance of reflux to their clinical course. The incidence of diagnosed GER was markedly higher in the years 1990 to 1995 compared with previous years, 1982 to 1989 (27.7% vs 13.5%). This finding may not be statistically significant because of the small number of patients. However, it is probable that recognition and diagnostic evaluation have improved in the past years, thus leading to a twofold higher incidence of confirmed GER compared with the earlier period; most likely, the true incidence from 1982 to 1989 was higher. On the basis of our findings, GER is to be expected in at least one of every five patients with SCID. Additionally, in the past 5 years markedly more children had a severe, complicated clinical course, did not respond to medical treatment, and thus underwent surgical intervention.

Table II shows the distribution of the three main symptoms of GER in patients with SCID. There was no consistent pattern of symptoms in our study population. The clinical presentation was heterogeneous with slight dominance of gastrointestinal problems: nine of 15 patients experienced frequent vomiting and esophagitis, of which three showed severe symptoms. Seven patients had recurrent respiratory problems; two of them had severe aspiration pneumonia. Though many of the patients had other respiratory symptoms, such as wheezing or cough, these symptoms were not used to support the diagnosis of GER because concurrent respiratory tract infections made it impossible to attribute them to reflux alone. Five children were suspected of having SCID because of poor feeding and failure to thrive. Of all children who underwent surgical correction at our institution, 6.6% were patients with severe immunodeficiency, despite the rarity of this diagnosis (Table III). GER causing symptoms and requiring surgical treatment was more common in children with SCID than in patients with functional abnormalities, cystic fibrosis, or asthma; and the number of children requiring surgery was equal to the number of premature infants. The majority of patients without SCID undergoing Nissen fundoplication had either anatomic abnormalities or congenital diseases, such as hydrocephalus and a variety of inborn errors of metabolism. Seven of 73 patients with SCID required surgery; it is not possible to determine the percentage of patients with any of the other diseases who underwent surgical correction because the preva-

TABLE II. Symptoms associated with GER in patients with SCID

Patient	Sex	Birth	Respiratory symptoms	GI symptoms	FTT/feeding problems
EJ	M	1982	+	-	-
BL	F	1982	-	+	-
TA	M	1983	++	+	-
BC	M	1984	-	-	+
SJ	M	1984	-	+	-
LR	M	1990	-	++	-
LB	M	1991	-	+	-
AC	M	1992	+	-	-
RJ	F	1992	-	+	++
RX	M	1992	+	++	+
SR	M	1992	++	-	-
BR	M	1994	+	+	-
MF	M	1994	+	-	++
JL	M	1995	-	++	-
MB	M	1995	-	-	+

Respiratory symptoms include aspiration pneumonia, and respiratory distress; GI symptoms include esophagitis vomiting.

GI, Gastrointestinal; FTT, failure to thrive; -, no symptoms; +, moderate symptoms; ++, severe symptoms.

TABLE III. Clinical abnormalities in 121 patients with GER who underwent Nissen fundoplication between 1990 and 1995

Type of abnormality	No.	Percent
Immunodeficiency (SCID, Di-George syndrome)	8	7
Anatomic (diaphragmatic and paraesophageal hernia, tracheoesophageal fistula, esophageal stricture and atresia, pyloric stenosis)	18	15
Functional abnormalities (esophageal dysmotility, dyskinesia, myopathy)	4	3
Congenital disorders (heart disease, inborn errors of metabolism, Downs-syndrome, other chromosomal anomalies, hydrocephalus, severe intracranial abnormalities)	33	27
Prematurity (preterm infants, intrauterine infections, parental drug abuse)	7	6
Infantile cerebral palsy (class II-III)	21	17
Cystic fibrosis	2	2
Not otherwise classified	28	23
Total	121	100

lence of these diseases is not known within the Duke patient population.

The clinical presentation of GER in patients with SCID treated with fundoplication was compared with that in the other high-risk groups; symptoms were listed according to the underlying basic disease, as shown in Table IV. We found that gastrointestinal symptoms were

the most dominant in patients with SCID (88%), as well as in the group with anatomic abnormalities (94%); whereas respiratory symptoms were seen in 38% and 50%, respectively. Only two patients of the group with anatomic abnormalities were first seen with failure to thrive, whereas four of eight patients with SCID (50%) showed significant developmental retardation. Patients with infantile cerebral palsy and premature infants had the most homogenous pattern and showed high percentages in all three major clinical symptoms. Children with congenital disorders other than SCID had a significantly higher frequency of respiratory and gastrointestinal symptoms compared with failure to thrive. Although not statistically significant because of the small number of patients, GER may therefore be an additional complicating factor to failure to thrive, which is a common finding in patients with SCID and is often attributed to infection.

DISCUSSION

Many factors may contribute to the pathogenesis of GER.^{6,12} Normally, the lower esophageal sphincter creates a pressure barrier against reflux of gastric contents. The extension of the circular smooth muscle at the gastroesophageal junction maintains a resting pressure between 15 and 40 mm Hg versus an intragastric pressure of approximately 6 to 10 mm Hg and an intrathoracic pressure that ranges between -6 and 10 mm Hg. Increased intraabdominal pressure (e.g., from crying, coughing, or defecating) has been shown to induce GER; thus, a chronically lax sphincter or frequent, spontaneous decreases in sphincter tone are important mechanisms in the cause of disease. Decreased lower esophageal pressure may be associated with anticholinergics, theophylline, caffeine, nicotine, alcohol, dopaminergics, epinephrine, and prostaglandins, as well as with some gastrointestinal hormones

TABLE IV. GER correlated to clinical symptoms in patients treated with fundoplication

Disorder	No.	Respiratory symptoms	GI symptoms	FTT
Anatomic abnormalities	18	9 (50%)	17 (94%)	2 (11%)
Functional abnormalities	4	4 (100%)	1 (25%)	0
Congenital disorders	33	29 (88%)	29 (88%)	9 (27%)
Prematurity	7	6 (86%)	6 (86%)	5 (71%)
Infantile cerebral palsy	21	20 (95%)	17 (81%)	10 (48%)
Immunodeficiency	8	3 (38%)	7 (88%)	4 (50%)
Cystic fibrosis	2	2 (100%)	2 (100%)	0
Other	28	25 (89%)	10 (36%)	12 (43%)

GI, Gastrointestinal; FTT, failure to thrive.

such as glucagon, secretin, cholecystokinin,¹² progesterone, and estrogen. Additionally, neurodevelopmental disorders, scleroderma, or delayed gastric emptying are factors leading to decreased lower sphincter tone.¹³ Other mechanisms such as increased gastric acid, trypsin, or pepsin secretion result in changes in the physiologic reflux rate and finally in esophageal damage. Anatomic changes (hiatal hernia, obesity, or gastric surgery) or poor esophageal clearance (e.g., peristaltic dysfunction or impaired salivation) may result in damage to the functional integrity of the esophagus.^{14, 15} None of these pathophysiologic factors, however, are necessarily present in children with severe congenital immunodeficiency. In fact, careful exploration of the patients' histories showed no evidence that one or more of these mechanisms had been noted by the physicians taking care of the children. Another possible mechanism for reflux, infectious inflammation of the esophagus (e.g., fungal esophagitis as reported in patients with AIDS),¹¹ was excluded because only children without a history of *Candida* or other infection of the pharynx, esophagus, or lungs were included in this study. Because all the forms of SCID are due to specific defects in lymphocyte development, there is no reason to consider multiorgan involvement in the etiology of GER in SCID, as seen in children with chromosomal defects or severely retarded patients in whom more than one organ system may be contributing to the condition.¹⁶ Therefore the underlying pathophysiologic of GER in patients with SCID is speculative.

In conclusion, GER has been noted in an unexpectedly high percentage of patients with SCID. The increased incidence between 1990 and 1995 is probably due to better recognition and improved diagnostic evaluation. The true incidence may be even higher because patients with mild symptoms are not evaluated or because their symptoms are attributed to infections, medications, or other causes.¹⁷ The symptoms of GER in patients with SCID reflect a heterogeneous pattern but can be masked by infections or side effects of medications and can therefore be misinterpreted. Our data suggest that one of every five pa-

tients with SCID will have reflux disease, thus complicating the already difficult clinical course of these children. It is also worth noting that in the past 5 years, markedly more children with GER needed surgical intervention because of failure of medical treatment than in the years before. Therefore it is recommended that these patients be carefully monitored with regard to reflux-related symptoms because early recognition and efficient management can prevent damage to the lungs and esophagus and enable adequate enteral nutrition.

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