

Rubinstein–Taybi syndrome: An immune deficiency as a cause for recurrent infections

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ABSTRACT

Rubinstein–Taybi Syndrome (RTS) is characterized by broad toes, broad thumbs, facial dysmorphisms, and mental retardation. The syndrome has been shown in some patients to be associated with break points in and microdeletions of chromosome 16p13.3. It is estimated that ~75% of patients with RTS experience recurrent respiratory infections. In this study, three patients thought to have RTS and recurrent infections were evaluated for an immunologic deficiency. All three patients showed a polysaccharide antibody response deficit. We conclude that a primary immune deficiency may exist in the remainder of the RTS population and may explain the reason for the propensity for recurrent infections. Aggressive investigation and management in patients with RTS may further determine the mechanism of this deficiency and enhance the quality of life of these patients.

(Allergy Asthma Proc 27:281–284, 2006; doi: 10.2500/aap.2006.27.2864)

Rubinstein–Taybi syndrome (RTS) is a rare condition initially described in 1963.¹ It is characterized by mental retardation, facial dysmorphisms, cardiac anomalies, broad thumbs, and great toes. The syndrome has been shown in some patients to be associated with break points in and microdeletions of chromosome 16p13.3. Approximately 73% of patients with RTS experience recurrent respiratory tract infections, including recurrent otitis media. It was thought that these infections were complications of structural abnormalities, microaspiration, and/or gastroesophageal reflux.

Although an immunodeficiency was suspected, no large immunologic studies were performed of this population. Three previous case reports suggested immunodeficits, but because of their differing immunologic evaluation methods these studies were difficult to compare.^{2,3}

One study suggested an antibody response deficit that was amenable to i.v. γ -globulin infusions.⁴ Further evaluation of two other patients with RTS suggested that this antibody deficit may be common in this syndrome but only may represent a smaller component of a more global lymphocytic abnormality.

CASE REPORTS

Method

The patients were evaluated by their primary care physician. The evaluation was performed as part of a normal immunologic workup. Local internal review board approval was obtained for this study.

Pre- and post-antipolysaccharide antibody titers were determined for 12 serotypes of pneumococcus and were performed by IBT Laboratories (Lenexa, KS). The patients were vaccinated with the 23-valent Pneumovax (Merck, Whitehouse Station, NJ). Post-titers were drawn 1 month after vaccination.

Patient 1 (Tables 1 and 2) is a 14-year-old boy who experienced several episodes of pneumonia, fever, otitis media, and sinusitis.⁴ Serum immunoglobulins were normal but antibody response to polysaccharide antigens was deficient.

Antibody titers to tetanus were normal. This patient was started on i.v. IgG replacement therapy and responded with fewer and less severe infections. Because of the low numbers of T cells (Table 3), he also was started on *Pneumocystis carinii* prophylaxis with trimethoprim-sulfamethoxazole. Mild functional T-cell deficiencies were noted to Con A, *Candida*, but were normal for phytohemagglutinin.

Patient 2 (Tables 1 and 2) is a 15-year-old boy who experienced chronic otitis media. He underwent tympanoplasty, mastoidectomy, and removal of a cholesteatoma. An immunologic evaluation showed a low IgA and also IgG2 subclass deficiency. A deficient response to polysaccharide antigens was noted; although preexisting titers were present, only four serotypes were >1.4 mg/dL and none were enhanced after vac-

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Table 1 Serum immunoglobulins

	Patient 1	Patient 2	Patient 3	Normal
IgG	710	1090	792	639–1704 mg/dL
IgA	247	<6.0	166	67–367 mg/dL
IgM	14	38	171	41–163 mg/dL
IgG1	528	942	475	165–1440 mg/dL
IgG2	66	21	256	71–460 mg/dL
IgG3	56	46	35	11–176 mg/dL
IgG4	14	11	30	2–1425 mg/dL
Tetanus	2.20	1.26	2.5	>0.15 IU/mL

cination. Antibody titers to tetanus were normal. Lymphocyte markers were normal (Table 3).

Patient 3 (Tables 1 and 2) is a 28-year-old man who experienced frequent otitis media and one episode of pneumonia. The ear infections were not alleviated by four sets of tympanostomy tubes. Infections persisted until the age of 28 years, his present age. He had normal lymphocytes for his age (Table 3). Serum immunoglobulins and IgG subclass levels were normal. Antibody responses to polysaccharide antigens were present but only three serotypes were >1.4 mg/dL and only one was enhanced after vaccination. Antibody response to tetanus was normal.

DISCUSSION

Rubinstein–Taybi syndrome is a clinically heterogeneous disorder encompassing several organ systems possibly linked to chromosome 16p13.3.^{5–7} The most prominent phenotypic structural abnormality in these patients is their broad thumbs and toes. They also have distinctive dysmorphic facial features that include palpebral fissures slanting down toward the ears, apparent hypertelorism, long eyelashes, high arched eyebrows, prominent nose with columella below the alae nasi, malpositioned ear with dysplastic helices, distinctive smile, highly arched palates, and hypoplastic maxillae.^{8,9} These structural abnormalities often have been referenced along with these patient's reflux potential as a predisposing cause of their recurrent respiratory infections.^{10,11}

Prominent upper and lower respiratory tract infections are experienced by patients with RTS.^{9,11,12} Their lives are complicated by the severity of these infections often requiring emergency room visits, outpatient visits, procedures, and hospitalizations. Several investigators have attempted to offer an immunologic reason for these recurrent infections. One group showed a defect of polymorphonuclear phagocytosis using a latex particle assay. In this same patient, there were decreased T-cell numbers using rosette formation, delayed hypersensitivity to multiple antigens, and normal serum immunoglobulins.²

Another group showed decreased thymic tissue at autopsy in one patient with RTS. Preautopsy showed that peripheral blood T cells were normal. They also noted that serum IgG levels were transiently diminished and serum IgA was low. No treatment of the foregoing deficiency was pursued.³

We described one patient with low T-cell numbers and function as well as absent antibody response to polysaccharide antigens. Antibodies to tetanus were present. This patient was started on i.v. γ -globulin therapy and dramatically improved.⁴

Because of this clinically effective response to therapy, two other patients with RTS were evaluated for an antibody response defect. These two were evaluated with consistently similar deficits of antibody production, although γ -globulin therapy was not instituted. In these two patients, preexisting antipolysaccharide antibody titers were present. These titers did not enhance or replicate after immunization.

Primary immunodeficiencies are a diverse group of disorders. They encompass abnormalities of T cell, neutrophil, complement, and B cell lineage. The most common of these deficits involve the B cell and their subsequent secretion of immunoglobulin. Over the past several years the evaluation of patients with recurrent respiratory tract infections has moved to functional responses of immunoglobulin synthesis (*i.e.*, antibody responses to protein and polysaccharide antigens). Protein antibody response is mediated through a T-cell-dependent pathway. Polysaccharide antigen response is a T-cell-independent process relying purely on B-cell maturity, clonality, and functionality. This response is tested *via* the evaluation of antibody response to 12 serotypes of pneumococcus after the vaccination with a commercially available vaccine (Pneumovax). After the vaccination, titers to these 12 serotypes should rise greater than twofold to be considered a response. If the responses are less than three serotypes, the patient is considered a nonresponder. These functional deficits often are found even in the presence of normal serum immunoglobulin and subclasses.¹³ At this level of immunologic evaluation, re-

Table 2 Antipolysaccharide antibody responses ($\mu\text{g/mL}$)

Serotype	Patient 1		Patient 2		Patient 3	
	Pre- Antipolysaccharide Antibody Titers	Post- Antipolysaccharide Antibody Titers	Pre- Antipolysaccharide Antibody Titers	Post- Antipolysaccharide Antibody Titers	Pre- Antipolysaccharide Antibody Titers	Post- Antipolysaccharide Antibody Titers
1	<0.3	0.4	1.0	1.1	1.4	1.1
3	<0.3	0.6	2.1	0.8	3.3	0.6
4	<0.3	0.6	1.3	0.2	1.4	0.8
6	<0.3	0.6	1.3	0.4	1.4	0.7
8	<0.3	0.6	2.1	2.6	1.4	1.0
9	<0.3	0.6	0.6	0.7	3.0	0.8
12	<0.3	0.6	0.7	0.3	1.4	0.2
14	<0.3	0.6	2.5	1.2	1.9	7.2
19	<0.3	0.6	0.9	0.5	1.8	2.4
23	<0.3	0.6	2.4	0.3	1.7	0.7
51	<0.3	0.6	1.3	1.1	3.4	0.6
56	<0.3	0.6	0.8	0.5	1.4	0.5

*More than 1.4 mg/dL is considered normal in pretiters. At least doubling of the preexisting titers in the post-titers is considered a response.

Table 3 Lymphocyte population

Markers	Patient 1	Patient 2	Patient 3	Normal
CD3 (%)	53	60	68	59–87%
CD3 no.	410	1190	1482	710–4180
CD4 (%)	29	41	54	29–57%
CD4 no.	230	810	1177	350–2740
CD8 (%)	20	16	13	7–31%
CD8 no.	160	320	283	80–1490
CD19 (%)	11	29	11	6–19%
CD19 no.	90	570	240	70–910

sponse to both protein and polysaccharide antigens may not be identically deficient. Because separate pathways are involved in the antibody formation process, a deficit may exist in one pathway and not the other.

Antipolysaccharide antibody deficiencies have been found as part of other primary immunodeficiency disorders. For example, patients with Wiskott-Aldrich syndrome fail to make specific isohemagglutinins.¹⁴ DiGeorge patients share this lack of antibody response to polysaccharide antigens.¹⁵ Similarly, patients with RTS may have a antipolysaccharide antibody deficiency that may be a smaller part of a more global immunologic defect.

It is estimated that B-cell defects including functional B-cell abnormalities exist in the general population in a prevalence of 1:10,000.¹⁶ There are an estimated 870 patients with RTS worldwide. Having found three individuals with RTS who lack an adequate antibody response to polysaccharide antigens suggests that this deficit may be one of the reasons for the recurrent respiratory tract infections in RTS.

Many patients with RTS have been shown to have breakpoints in and microdeletions of chromosome 16p13.3. These break points are restricted to a region that contains the gene for the human CREB binding protein (CBP), a nuclear protein participating as a co-activator in cyclic-AMP-regulated gene expression. RTS results not only from chromosomal rearrangements of chromosome 16p, but also from point mutations in the CBP gene.¹⁷ CBP is a critical transcriptional regulator. It is required for the effective function of a variety of transcriptional systems including NF- κ B. Defects in this regulatory system have been linked to other primary immunodeficiencies.¹⁸ Additional research is needed to determine if defects in this regulatory mechanism are responsible for the more global immunodeficiency proposed in RTS.

We have described three individuals with RTS with recurrent infections each having similar immunologic deficiencies. These data suggest that this defect could be a major cause for recurrent infections in these pa-

tients. Treatment with i.v. γ -globulin of some at a dose of 400 mg/kg monthly may prevent further infections in this population that is already afflicted with other systemic abnormalities.

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