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Immune Abnormalities Are a Frequent Manifestation of Kabuki Syndrome

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Kabuki syndrome (KS) is associated with multiple organ system involvement. Characteristic features include long palpebral fissures with everted lower lids, prominent ears, skeletal abnormalities, mental retardation, and short stature. An increased incidence of infection has been reported in KS, and a few patients have been noted to have immune defects. However, the frequency and severity of the immune deficiency has not been clearly defined. Immunologic evaluation of 19 consecutive individuals with KS was performed at The Children's Hospital of Philadelphia. Decreased IgA levels were noted in 15/19 individuals (79%), 2 of whom had undetectable levels. Eight patients (42%) also had low total IgG levels. Specific IgG subclass abnormalities were found in 6 of 13 patients evaluated. IgM levels were less frequently decreased. One patient failed to generate anti-tetanus antibodies despite immunization. This study suggests that hypogammaglobulinemia is a frequent finding in children with KS. The pattern of antibody abnormalities seen in children with KS resembles common variable immune deficiency (CVID). Due to this increased susceptibility to infection, children with KS should have immunologic evaluations at the time of diagnosis in order to reduce preventable morbidity and mortality.

KEY WORDS: Kabuki syndrome; hypogammaglobulinemia; immunoglobulins; common variable immune deficiency; immunodeficiency

INTRODUCTION

Kabuki syndrome (KS), or Niikawa–Kuroki syndrome, is a condition of unclear etiology associated with multiple organ system involvement. It was initially described in Japanese patients [Kuroki et al., 1981; Niikawa et al., 1981], and the phenotype has since been described in multiple ethnic groups [Philip et al., 1992; Schrander-Stumpel et al., 1994; Kawame et al., 1999; Shotelersuk et al., 2002]. Frequent features of KS include long palpebral fissures with eversion of the lower lids, arched eyebrows, prominent ears, congenital heart defect, cleft palate, skeletal abnormalities, mental retardation, and short stature.

Recurrent infections, most often otitis media and pneumonia, have been noted in multiple KS patients. A susceptibility to infection is estimated to affect 60%–73% of patients with KS [Niikawa et al., 1981; Philip et al., 1992; Schrander-Stumpel et al., 1994]. However, the cause of the frequent infections is not clear. Of note, several patients have had hypogammaglobulinemia, most often affecting IgA and/or IgG [Hostoffer et al., 1996; Artigas et al., 1997; Chrzanowska et al., 1998; Ewart-Toland et al., 1998; Kawame et al., 1999; Shotelersuk et al., 2002].

Overall, the frequency and severity of immune deficiency have not been defined in patients with KS. We first present a patient with KS who had severe consequences of immune deficiency. We then present the results of an immunologic evaluation of 19 unselected additional patients with KS.

MATERIALS AND METHODS

Patients

The patient described in the clinical report was evaluated by two of the authors (J.M., E.H.Z.). In addition, a series of 19 additional patients diagnosed with KS based on examinations by the authors (J.E.M., E.H.Z., P.B.K.) underwent immunologic evaluation. Identifying facial features included long palpebral fissures with everted lower lids, thinning of the eyebrows, prominent eyelashes, prominent auricles, and a depressed nasal tip. The patients ranged in age from 1 to 20 years of age. Ten patients were female and nine were male. Fifteen patients were Caucasian, three were Hispanic, and one was of Moroccan ancestry. Some features of some of the patients have been previously described [Ming et al., 2005]. The medical records of each patient were reviewed for episodes of infections including otitis media, pneumonia, respiratory syncytial virus infection, urinary tract infections, and other significant infections.

Immunologic Evaluation

Quantitative serum analysis for IgA, total IgG, and IgM was performed in each of 19 consecutive patients with KS, without regard to previous infection status. Thirteen of the 19 children also had IgG subclass analysis and anti-tetanus titer analysis performed. Three patients also had lymphocyte subset studies performed.

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RESULTS

Clinical Report

The patient was a 35-year-old male with KS. He had short stature, mental retardation, submucous cleft palate, hypodontia, and lower lip pits. On exam, he had prominent eyelashes, thinned eyebrows, and persistent fingertip pads. His karyotype was 46,XY, and subtelomeric analysis was normal. He had a history of idiopathic thrombocytopenia purpura (ITP). He had a history of recurrent pneumonia, urinary tract infections, chronic recurrent otitis media, and sinusitis since childhood. Upon hospitalization for pneumonia at 35 years of age, he was noted to have markedly decreased serum total IgG level of 33 mg/dl (normal 639-1,349 mg/dl) and an IgA level of 7 mg/dl (normal 70–312 mg/dl). He also had a mildly decreased IgM level of 48 mg/dl (normal 56–352 mg/dl). Despite treatment with antibiotics and immunoglobulin, he died from complications of pneumonia and an idiopathic reaction to intravenous immune globulin therapy.

Immune Studies in a Series of 19 KS Patients

A systematic examination of the frequency and type of immune deficiency present in KS was pursued through analysis of immunoglobulin levels in 19 consecutive patients diagnosed with KS and evaluated at The Children's Hospital of Philadelphia. The frequency figures indicated in this report are based on the analysis of these 19 patients and do not include the immune results of the patient described in the clinical report. Sixteen of the 19 children had some form of decreased antibody level (84%) (Table I). Fifteen (79%) of these patients had decreased IgA levels, including two patients with undetectable IgA levels, and an additional five patients had IgA levels between 10 and 20 mg/dl. Also, two of the four patients with a normal IgA level had a level in the bottom 1% of the normal range. Eight patients had decreased total IgG (42%). In two of these eight patients, the IgG level was less than one-half of the lower limit of normal for age. IgG subclass quantitation was obtained on 13 patients. Specific IgG subclass abnormalities were found in 6 of these 13 patients, all of whom also had IgA deficiency. No patient was found to have IgG2 or IgG4 subclass deficiency. Two patients had a slightly decreased IgM level. Both of these patients had decreased IgA levels as well. Twelve patients were tested for anti-tetanus antibody titer, and one was found to be deficient despite having received all appropriate vaccinations at age three. Lymphocyte subtype studies were performed on three patients, and no abnormalities were noted in the number or proportion of $CD19^+$, $CD3^+$, $CD4^+$, or $CD8^+$ cells.

DISCUSSION

Increased susceptibility to infection has been described as a common feature of KS. We sought to determine the frequency and severity of immune abnormalities in KS. Our analysis of 19 consecutive affected patients demonstrates that hypogammaglobulinemia is a much more frequent manifestation of KS than previously recognized. The immune findings in KS are similar to those seen in common variable immune deficiency (CVID). CVID is an etiologically heterogeneous immune disorder whose etiology is not yet clearly defined. It is characterized by hypogammaglobulinemia, the presence of B cells, and normal or near-normal T cell immunity [Cunningham-Rundles, 2001]. The incidence is between 1 in 25,000 and 1 in 66,000 [Hammarstrom et al., 2000]. Patients often present in the 2nd to 4th decades of life with long histories of recurrent respiratory infections, otitis media, and gastrointestinal infections. The immune defect is variable. Decreased serum IgA level is the most common finding, and most patients have

TABLE I. Immune Studies of 19 Children With Kabuki Syndrome (KS)

Patient	Age	Gender	IgA	Total IgG	IgG subclasses	IgM	Anti-tetanus titer	Infection history
1	3 y 2 m	Male	→	→	—	nl	Absent	Pneumonia, recurrent diarrhea, skin abscesses
2	1 y 5 m	Female	→	nl	↓ IgG3	nl	nl	Recurrent OM, RSV, UTI
3	1 y	Female	↓↓↓	↓↓	↓ IgG1	nl	—	Unremarkable
4	11 y 8 m	Female	→	nl	nl	nl	—	Chronic OM, and sinusitis, conjunctivitis, C. diff diarrhea
5	4 y 10 m	Male	nl	nl	—	nl	nl	OM, C. diff diarrhea
6	20 y 11 m	Female	↓↓↓	nl	—	nl	nl	Recurrent OM and UTI
7	18 y	Male	→	nl	↓ IgG1	nl	nl	Recurrent OM
8	7 y 8 m	Female	↓↓	→	↓ IgG1	nl	—	OM, pneumonia, cutaneous fungal infection
9	1 y 1 m	Male	→	nl	↓ IgG3	nl	—	Recurrent OM and pneumonia
10	9 y 2 m	Female	↓↓	→	↓ IgG3	nl	nl	Recurrent OM, sinusitis, UTI
11	15 y 4 m	Male	↓↓	→	—	nl	nl	Recurrent OM, sinusitis
12	4 y 7 m	Female	nl	→	nl	nl	—	Recurrent OM
13	1 y 6 m	Male	→	nl	nl	→	nl	Recurrent OM, pneumonia, strep throat, fungal toenail infection
14	7 y 3 m	Male	↓↓	nl	nl	nl	nl	Pneumonia
15	12 y 11 m	Female	nl	nl	nl	nl	—	Recurrent OM, pneumonia, UTI, Lyme disease
16	3 y 8 m	Female	→	nl	nl	nl	nl	Unremarkable
17	9 y 7 m	Male	↓↓	↓↓	—	→	—	OM
18	4 y 10 m	Male	nl	nl	—	nl	nl	Pneumonia
19	7 y 8 m	Male	↓↓	→	nl	nl	nl	Recurrent OM
Abnormal total (%)			15/19 (79%)	8/19 (42%)	6/13(46%)	2/19 (10%)	1/12(8%)	

y, year(s); m, month(s); —, not tested; ↓↓↓, absent; ↓↓, less than 50% of lower limit of normal for age; ↓, slightly decreased; nl, normal; (ranges according to age and laboratory available on request); OM, otitis media; RSV, respiratory syncytial virus infection; UTI, urinary tract infection; C. diff, C. difficile infection.

TABLE II. Previous Reports of Immune Dysfunction in KS

Patient	Gender	Age	IgA level	IgG level	IgM level	Autoimmune diseases	Reaction to IVIG	Reference
1	Female	11 y	Low	—	—	Recurrent thrombocytopenia	—	Artigas et al. [1997]
		13 y	Low	Low	Low	ITP		
2	Male	10 y	Low-absent	Low-absent	Normal-low	—	—	Chrzanowska et al. [1998]
		19 y	Low-absent	Low	Low		—	
3	Female	19 m	Low	—	—		Anaphylaxis	Hostoffer et al. [1996]
		3 y	—	—	—	Recurrent ITP		
		5 y	—	—	—			
		9 y	Low-absent	Low-absent	Low-absent	Absent reaction to vaccines		
4	Female	10 m	Low	Normal	Normal	—	—	Shotelersuk et al. [2002]
5	Female	12 y	Low-absent	—	—	Hemolytic anemia, thrombocytopenia	none	Kawame et al. [1999]
		14 y	Low-absent	Low	Low	Absent reaction to vaccines		
6	Female	6 y	Low-absent	—	—	Hashimoto's thyroiditis, Vitiligo	—	Ewart-Toland et al. [1998]

y, years; m, months; —, not reported.

decreased total IgG levels. A low level of IgM can be present but is a less frequent finding. Patients with CVID often have a normal number of B lymphocytes, but may have defective B lymphocyte maturation to plasma cells. The higher levels of IgM compared to other immunoglobin types may be due to a defect in antibody class-switching. In addition, the immune defects in CVID may worsen with time [Cunningham-Rundles, 2001]. Due to the variable expression of immune dysfunction seen in CVID, the diagnosis of CVID in the general population is often delayed.

Due to the increased incidence of immune abnormalities in children with KS, serum immunoglobulin levels should be determined at the time of diagnosis for children over 1 year of age. For children less than 1 year of age, maternal IgG contribution and immaturity of the immune system may make interpretation of immune studies problematic. It may also be important to test vaccine titers to determine immune status after vaccinations. Due to the similarity of the immune defects in KS and CVID, it is possible that immunoglobulin levels in a child with KS may initially be normal but later become abnormal. It is therefore recommended that immunoglobulin studies be repeated at scheduled intervals. We also recommend that testing include patients without a clinical history strongly suggestive of immune deficiency in order to assess immune status and identify patients presymptomatically, potentially preventing significant morbidity and mortality. It is also possible that recurrent infections may become more evident with age. Since many reports of KS patients are of younger children, the frequency of serious infections may be higher than previously recognized. Patients with KS and immunoglobulin abnormalities should be referred to an immunologist for a complete evaluation.

Treatment for hypogammaglobulinemia may include administration of intravenous immunoglobulins (IVIG). Of note, IVIG precipitates may contain significant quantities of IgA. Anti-IgA antibodies were identified in the serum of a 9-year-old girl with KS [Hostoffer et al., 1996]. Due to the increased frequency of adverse reactions to IVIG, as seen in the patient in the Case Report as well as Table II, it is important to give IVIG infusions in a closely monitored setting, at a low infusion rate, and after appropriate premedication, including systemic antihistamine agents.

CVID is also associated with an increased risk of autoimmune disease [Cunningham-Rundles, 2001; Blanchette, 2002]. Of note, autoimmune disease occurs with increased frequency in KS, including ITP, autoimmune hemolytic anemia, thyroiditis, and vitiligo [Nako et al., 1984; Schrander-Stumpel et al., 1993; Watanabe et al., 1994; Hostoffer et al., 1996; Artigas et al., 1997; Ewart-Toland et al., 1998; Kawame et al., 1999; McGaughran et al., 2001; Ming et al., 2005]. Of note a number of the patients with autoimmune disorders also had laboratory evidence of an immune defect [Hostoffer et al., 1996; Artigas et al., 1997; Kawame et al., 1999; Ming et al., 2005]. It is estimated that 20%–25% of patients with CVID will develop an autoimmune disease [Cunningham-Rundles, 2001; Blanchette, 2002].

In summary, children with KS have an increased incidence of hypogammaglobulinemia. This immune defect is a frequent finding and is more common than previously recognized in KS. The hypogammaglobulinemia shares some characteristics with CVID. In order to decrease preventable morbidity and mortality, we recommend an immunologic evaluation at the time of diagnosis followed by regular immunologic monitoring. We also recommend caution when administering IVIG to individuals with KS due to potential adverse reactions to the IgA component. We expect that the elucidation of the genetic etiology of KS will further increase our understanding of the immune dysfunction and allow for better management and treatment in the future.

REFERENCES

Artigas M, Alcazar R, Bel J, Fernandez P, Javier G, Ortega E, Pintos G, Venderell T, Prats J. 1997. Kabuki syndrome and common variable immunodeficiency. Am J Hum Genet 61(suppl):A91.

Blanchette V. 2002. Childhood chronic immune thrombocytopenic purpura (ITP). Blood Rev 16:23–26.

Chrzanowska KH, Krajewska-Walasek M, Kus J, Michalkiewicz J, Maziarka D, Wolski JK, Brecevic L, Madalinski K. 1998. Kabuki (Niikawa–Kuroki) syndrome associated with immunodeficiency. Clin Genet 53:308–312.

Cunningham-Rundles C. 2001. Common variable immunodeficiency. Curr Allergy Asthm Rep 1:421–429.

Ewart-Toland A, Enns GM, Cox VA, Mohan GC, Rosenthal P, Golabi M. 1998. Severe congenital anomalies requiring transplantation in children with Kabuki syndrome. Am J Med Genet 80:362–367.

Hammarstrom L, Vorechovsky I, Webster D. 2000. Selective IgA deficiency (SIgAD) and common variable immunodeficiency (CVID). Clin Exp Immunol 120:225–233.

Hostoffer RW, Bay CA, Wagner K, Venglarcik J III, Sahara H, Omair E, Clark HT. 1996. Kabuki make-up syndrome associated with an acquired hypogammaglobulinemia and anti-IgA antibodies. Clin Pediatr 35:273–276.

Kawame H, Hannibal MC, Hudgins L, Pagon RA. 1999. Phenotypic spectrum and management issues in Kabuki syndrome. J Pediatr 134: 480–485.

Kuroki Y, Suzuki Y, Chyo H, Hata A, Matsui I. 1981. A new malformation syndrome of long palpebral fissures, large ears, depressed nasal tip, and skeletal anomalies associated with postnatal dwarfism and mental retardation. J Pediatr 99:570–573.

McGaughran J, Aftimos S, Jefferies C, Winship I. 2001. Clinical phenotypes of nine cases of Kabuki syndrome from New Zealand. Clin Dysmorphol 10:257–262.

Ming JE, Russell KL, McDonald-McGinn DM, Zackai EH. 2005. Autoimmune disease in Kabuki syndrome. Am J Med Genet 132A: 260–262.

Nako Y, Maruyama K, Sakaguchi M, Kuroki M, Terao K, Kuribayashi T, Ohshima Y, Nagahshima K, Tamura H. 1984. Two cases of autoimmune hemolytic anemia: A case associated with Kabuki make-up syndrome and a case with IgD as an anti-erythrocyte autoantibody. J Jpn Pediatr Soc 88:234–241.

Niikawa N, Matsuura N, Fukushima Y, Ohsawa T, Kajii T. 1981. Kabuki make-up syndrome: A syndrome of mental retardation, unusual facies, large and protruding ears, and postnatal growth deficiency. J Pediatr 99:565–569.

Philip N, Meinecke P, David A, Dean J, Ayme S, Clark R, Gross-Kieselstein E, Hosenfeld D, Moncla A, Muller D, Porteous M, Santos H, Cordeiro I, Selicorni A, Silengo M, Tariverdian G. 1992. Kabuki make-up (Niikawa–Kuroki) syndrome: A study of 16 non-Japanese cases. Clin Dysmorphol 1:63–77.

Schrander-Stumpel C, Theunissen P, Hulsmans R, Fryns JP. 1993. Kabuki make-up (Niikawa–Kuroki) syndrome in a girl presenting with vitiligo vulgaris, cleft palate, somatic and psychomotor retardation and facial dysmorphism. Genet Counsel 4:71–72.

Schrander-Stumpel C, Meinecke P, Wilson G, Gillessen-Kaesbach G, Tinschert S, Konig R, Philip N, Rizzo R, Schrander J, Pfeiffer L, Maat-Kievit A, van der Burgt I, van Essen T, Latta E, Hillig U, Verloes A, Journel H, Fryns JP. 1994. The Kabuki (Niikawa–Kuroki) syndrome: Further delineation of the phenotype in 29 non-Japanese patients. Eur J Pediatr 153:438–445.

Shotelersuk V, Punyashthiti R, Srivuthana S, Wacharasindhu S. 2002. Kabuki syndrome: Report of six Thai children and further phenotypic and genetic delineation. Am J Med Genet 110:384–390.

Watanabe T, Miyakawa M, Satoh M, Abe T, Oda Y. 1994. Kabuki make-up syndrome associated with chronic idiopathic thrombocytopenic purpura. Acta Paediatr Japon 36:727–729.