Antibody deficiency in Wolf-Hirschhorn syndrome

Jean Hanley-Lopez, MD, Laurel L. Estabrooks, PhD, and E. Richard Stiehm, MD

We identified antibody deficiencies in 9 of 13 infection-prone children with the Wolf-Hirschhorn syndrome (4p-monosomy). Eight of the immunodeficient children were identified by a questionnaire sent to 190 families with an affected child. Two of the children had common variable immunodeficiency, one had IgA and IgG2 subclass deficiency, three had IgA deficiency, and three had impaired polysaccharide responsiveness. T-cell immunity was normal. The association of antibody defects with Wolf-Hirschhorn syndrome suggests a regulatory gene within the deleted chromosome region that affects the B cell system. (J Pediatr 1998;133:141-3)

The Wolf-Hirschhorn syndrome is a genetic disorder with characteristic facial features, growth retardation, developmental delay, and skeletal and cardiac abnormalities. First described by Cooper and Hirschhorn[1] in 1961 and Wolf et al.[2] in 1995, it is associated with a partial deletion of the distal short arm of chromosome 4, specifically 4p16.3. This deletion arises de novo in 90% of the cases; in 10% of the cases it is inherited as a result of a translocation.[3] Nearly 130 cases have been reported.[3]

Although respiratory infections often accompany WHS, they have been attributed to hypotonia, recurrent aspiration, or gastroesophageal reflux. Aspiration pneumonia is common, and many of the children need continuous antibiotic therapy.

Our initial patient was a 3-year-old with WHS who was referred to us because of severe hypogammaglobulinemia. After making a diagnosis of common variable immunodeficiency in this patient, we placed a notice in the WHS parent support group newsletter (Dancing with Wolves) requesting that parents whose WHS children had problems with infections should contact us. Approximately 190 families received the publication, and 12 responded. Immunologic studies in these patients were performed. Along with our initial patient, a total of nine patients were identified with antibody defects. This extraordinarily high incidence of antibody deficiency suggest that WHS, like several other genetic syndromes,[4] may have an antibody deficiency as a frequent component of the illness.

From the Division of Immunology, UCLA Children's Hospital, Los Angeles, California, and Genzyme, Santa Fe, New Mexico.

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Reprint requests: E. Richard Stiehm, MD, UCLA Children's Hospital, 22-387-MDCC, 10833 Le Conte Ave., Los Angeles, CA 90095-1752.

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Results

R. H. (case 1) in the Table is the patient who initiated this study. Her medical history was similar to that of the other children with WHS presented in the Table. She had a severe episode of varicella at 9 months of age. At 3 years she had recurrent otitis media, sinusitis, chronic cough, and three bouts of pneumonia. Other problems included cardiac septal defects, gastroesophageal reflux, and seizures. Her mother had asthma, but there was no family history of immunodeficiency. Physical examination revealed characteristic dysmorphic facies, hypotonia, minimal tonsillar tissue, and no palpable lymph nodes. She was less than the 5th percentile in height and weight. As seen in the Table, at age 3 years immunoglobulins were low, antibody responses were absent, and B-cell numbers (CD19) were low. After monthly intravenous Ig infusions were started, the patient had fewer infections and improved weight gain.

WHS	Wolf-Hirschhorn syndrome
IVIG	Intravenous immunoglobulin

The clinical and laboratory features in the other children with WHS and antibody deficiency are shown in the Table. Their diagnoses included two patients with common variable immunodeficiency, one with combined IgA and IgG2 subclass deficiency, three with partial IgA deficiency, and three with impaired polysaccharide responsiveness.[5] All 13 children reviewed had characteristic clinical features such as microcephaly, growth retardation, development delay, orthopedic abnormalities, hypotonia, and karyotypic analysis that confirmed the diagnosis. Many had seizures, and nine were receiving anticonvulsive therapy including three of four in the control group. These latter children had recurrent respiratory infections but normal antibody systems as judged by normal or elevated immunoglobulins, antibody titers, or both.

Although all patients had deletions in the 4p16.3 region, there were different 4p breakpoints and various amounts of 4p deleted in the patients (data not shown). No correlation was noted between the immunologic abnormalities and the cytogenetic analyses including those with intact antibody immunity. Two immunodeficient patients had additional chromosomal im-

Table. Clinical and laboratory features of nine children with Wolf-Hirschhorn syndrome and antibody deficiencies

Patient ID	Age and sex	Infections	IgG*	IgM*	IgA*	IgE*	Other studies*	Lymphocyte subsets (%)†	Treatment
Hypogammaglobulinemia									
1. RH	3 yr F	OM, sinusitis, bronchitis, pneumonia, severe varicella	111	45	<12	<5	IgG1=80,2=12, 3=6, 4= <1	CD3=2785(74%) CD4=1392(37) CD8=1279(34) CD19=264(7)	IVIG Phenytoin
2. EF	22 mo M	OM, sinusitis, bronchitis, bronchiolitis, pneumonia, severe varicella	216	26	7	0	Tet, H.flu Abs neg. ConA, PHA stimulation normal	CD3=6710(61) CD4=4400(40) CD8=1980(18) CD19=3080(28)	IVIG PE tubes
IgG2 subclass and IgA deficiency									
3. JF	5 yr M	OM, sinusitis, nasolacrimal duct obstruction	644	77	<6	—	IgG1=603,2=2, 3=44,4=2		IVIG
Partial IgA deficiency									
4. GK	3 yr M	OM, sinusitis, pneumonia	822	27	18	0		Continuous antibiotics	
5. NL	17 mo M	Sinusitis, pneumonia, bronchitis	589	45	20	2.5		PE tubes	
6. TH	3 yr F	OM, sinusitis, bronchitis, pneumonia, severe varicella	636	113	11	14	IgG1=518,2=144, 3=50,4=30,Diph, Tet, H.flu Abs nl	Phenytoin	Continuous antibiotics PE tubes
Partial antibody deficiency									
7. SS	5.5 yr F	OM, sinusitis, nasolacrimal duct obstruction, recurrent severe herpes simplex	758	64	75	0.8	IgG1=498,2=174, 3=19,4=59,H.flu, Pneumococcal Ab low	CD3=2750(71) CD4=1350(35) CD8=1350(35) CD19=706(32)	IVIG Continuous antibiotics PE tubes
8. PD	5 yr F	OM, sinusitis, pneumonia, skin abscesses	690	54	37	—	IgG1=560,2=92, 3=31,4=74, H. flu Ab nl., pneumococcal Ab undetectable	CD3=1191(54) CD4=684(31) CD8=441(20) CD19=706(32)	
9. AC	3 yr F	Sinusitis, pneumonia	745	127	118	—	IgG1=557,2=149, 3=48, 42=4, pneumococcal, H. flu, Tet Ab low	CD3=2242(57) CD4=1546(39) CD8=555(14.1) CD16/56=201(5.1) CD19=1369(35)	Continuous antibiotics

IVIG, Intravenous immunoglobulin; *OM*, Otitis media; *H.flu*, *H. influenzae* (after conjugated vaccine.
*IgG, IgM, IgA, IgG subclass mg/dl; IgE IU/ml.
†Cells/mm^3.

balances, which may complicate the phenotypic presentation. One had an unstable ring 4 chromosome (case 3), reflecting the 4p deletion, a distal 4q deletion, and a "ring syndrome phenotype" caused by chromosomal instability. Another patient (case 6) had a deletion 4, +derivative (4)t(4;?)(p15.3,?). The origin of the other chromosomal material involved in the rearrangement was never identified, and the parental chromosome status is unknown. Her phenotype most likely reflects both the 4p deletion and the duplication of this other material.

DISCUSSION

The occurrence of common variable immunodeficiency, IgA deficiency, IgG subclass deficiency, or polysaccharide unresponsiveness in the WHS explains why many of these children have recurrent respiratory or viral infections. Most patients with WHS have hypotonia, neuromuscular abnormalities, and respiratory tract structural abnormalities that contribute to their susceptibility to respiratory infection. Several of the immunodeficient patients improved considerably with IVIG infusions or continuous antibiotics.

The immune deficiency in all nine children involved the B-cell system, but in

only one instance were B-cell numbers low (case 1). The association between common variable immunodeficiency and IgA deficiency in families has been observed,[6] and an association among IgA deficiency, IgG2 deficiency, and polysaccharide nonresponsiveness is well described.[7,8] Thus it is tempting to speculate that a single genetic abnormality leads to the immune impairment involving B-cell development and antibody responses. Alternatively, an antigenic processing defect may be present, similar to that postulated in the Wiskott-Aldrich syndrome[9]; this may explain why some of these patients have normal immunoglobulin levels despite repeated respiratory infections. Partial IgA deficiency (e.g., <2 SD below mean but yet detectable) as noted in patients 4 and 5 may occasionally be maturational and improve with age.[6] The association between common variable immunodefiency and IgA deficiency in certain families has been associated with certain human leukocyte antigen haplotypes and C4A null allele or rare C2 alleles controlled by major histocompatability complex genes on chromosome 6.[10]

The association of immunodeficiency with genetic disorders is not uncommon. Ming et al.[4] identified 64 genetic syndromes associated with immunodeficiency in addition to those genetic syndromes (e.g., Wiskott-Aldrich syndrome, ataxia-telangiectasia) with consistent immunologic defects (the primary immunodeficiencies). The immunologic abnormality in most of these genetic defects involve the T-cell system, but 16 had predominantly antibody defects. Many are associated with chromosome abnormalities, notably IgA deficiency with chromosome 18 deficiency and DiGeorge anomaly with 22q11 deletions.[4]

There was no apparent breakpoint correlation or suggestion of a distinct critical region for immunodeficiency. Because patients with both smaller and larger deletions had immunodeficiency, this would support a correlation with deletion of the common region 4p16.3. Explanations for the apparent reduced penetrance of the immunodeficiency trait could include assay sensitivity, age-related expression, and effect of other genes on trait presentation.

The very high frequency of immunologic abnormalities in these 13 patients (9 of 13) suggest this is not a chance occurrence of rare conditions. Even if we use an estimate of 190 children contacted in the United States, this incidence (9 of 190) is extraordinarily high. IgA deficiency occurs in 1 of 400 individuals and common variable immunodeficiency in 1 of 100,000.[11] Seven of the nine children with WHS were receiving anticonvulsants including two receiving phenytoin (cases 1 and 6), which is known to cause antibody deficiency, particularly IgA deficiency.[12]

No known genes affecting the immune system reside on the short arm of chromosome 4. Genes for Huntington's Disease, night blindness, and mucopolysaccharidosis are in this area, but none is known to be associated with immunodeficiency.[3]

In conclusion, B-cell defects have been identified in 9 of the 13 children with WHS. Because these children may benefit from IVIG infusions or continuous antibiotics, other children with WHS should be tested for immunodeficiency. The reason for this association is unknown, because no genes in the area of the deletion are known to be concerned with B-cell development.

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