

AUTOSOMAL RECESSIVE HYPERIMMUNOGLOBULIN E SYNDROME: A DISTINCT DISEASE ENTITY

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Objective The autosomal-dominant form of the hyperimmunoglobulin E syndrome (AD-HIES) has been described as a multisystem disorder including immune, skeletal, and dental abnormalities. Variants of AD-HIES are known but not well defined.

Methods We evaluated 13 human immunodeficiency virus-seronegative patients from six consanguineous families with an autosomal-recessive form of hyperimmunoglobulin E syndrome (AR-HIES) and 68 of their relatives.

Results Persons affected with AR-HIES presented with the classical immunologic findings of hyperimmunoglobulin E syndrome, including recurrent staphylococcal infections of the skin and respiratory tract, eczema, elevated serum immunoglobulin E, and hypereosinophilia. In addition, severe recurrent fungal and viral infections with molluscum contagiosum, herpes zoster, and herpes simplex were noted. Autoimmunity was seen in two patients. Central nervous system sequelae, including hemiplegia, ischemic infarction, and subarachnoid hemorrhages, were common and contributed to high mortality. Notably, patients with AR-HIES did not have skeletal or dental abnormalities and did not develop pneumatoceles, as seen in AD-HIES. In lymphocyte proliferation assays, patients' cells responded poorly to mitogens and failed to proliferate in response to antigens, despite the presence of normal numbers of lymphocyte subpopulations.

Conclusion The autosomal-recessive form of hyperimmunoglobulin E syndrome is a primary immunodeficiency with elevated immunoglobulin E, eosinophilia, vasculitis, autoimmunity, central nervous system symptoms, and high mortality. AR-HIES lacks several of the key findings of AD-HIES and therefore represents a different, previously unrecognized disease entity. (*J Pediatr* 2004;144:93-9)

P rimary immunodeficiencies with elevated immunoglobulin (Ig) E are rare and include hyper-IgE syndrome, Wiskott-Aldrich syndrome, Omenn syndrome, and Netherton-Comèl syndrome (all reviewed in Grimbacher et al¹). The hyper-IgE syndrome (HIES; OMIM #147060), also known as *Job syndrome* (OMIM #243700), is a multisystem disorder of unknown cause that affects the immune system, skeleton, connective tissue, and dentition.² The immune phenotype of HIES is characterized by recurrent staphylococcal infections of the skin and lungs, pneumatocele formation, eczema, candidiasis, eosinophilia, and elevated levels of IgE.²⁻⁸ Nonimmunologic features of HIES, seen in a cohort of patients with HIES, include in decreasing frequency characteristic facial appearance,^{2,9} scoliosis, retained primary dentition, joint hyperextensibility, recurrent bone fractures after minimal trauma, and craniosynostosis.^{2,10-12} Most cases of HIES are sporadic. However, multiplex kindreds most consistent with autosomal-dominant

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Supported by a grant of the Deutsche Forschungsgemeinschaft GR-1617/2, and the fellowship of the Immune Deficiency Foundation, Towson, Maryland (to B. G.).

Submitted for publication Aug 23, 2002; revision received Mar 13, 2003; accepted July 15, 2003.

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10.1016/S0022-3476(03)00449-9

AD-HIES	Autosomal-dominant hyperimmunoglobulin E syndrome	CT	Computed tomography
AR-HIES	Autosomal-recessive hyperimmunoglobulin E syndrome	HIES	Hyperimmunoglobulin E syndrome
		Ig	Immunoglobulin
CNS	Central nervous system	MRI	Magnetic resonance imaging

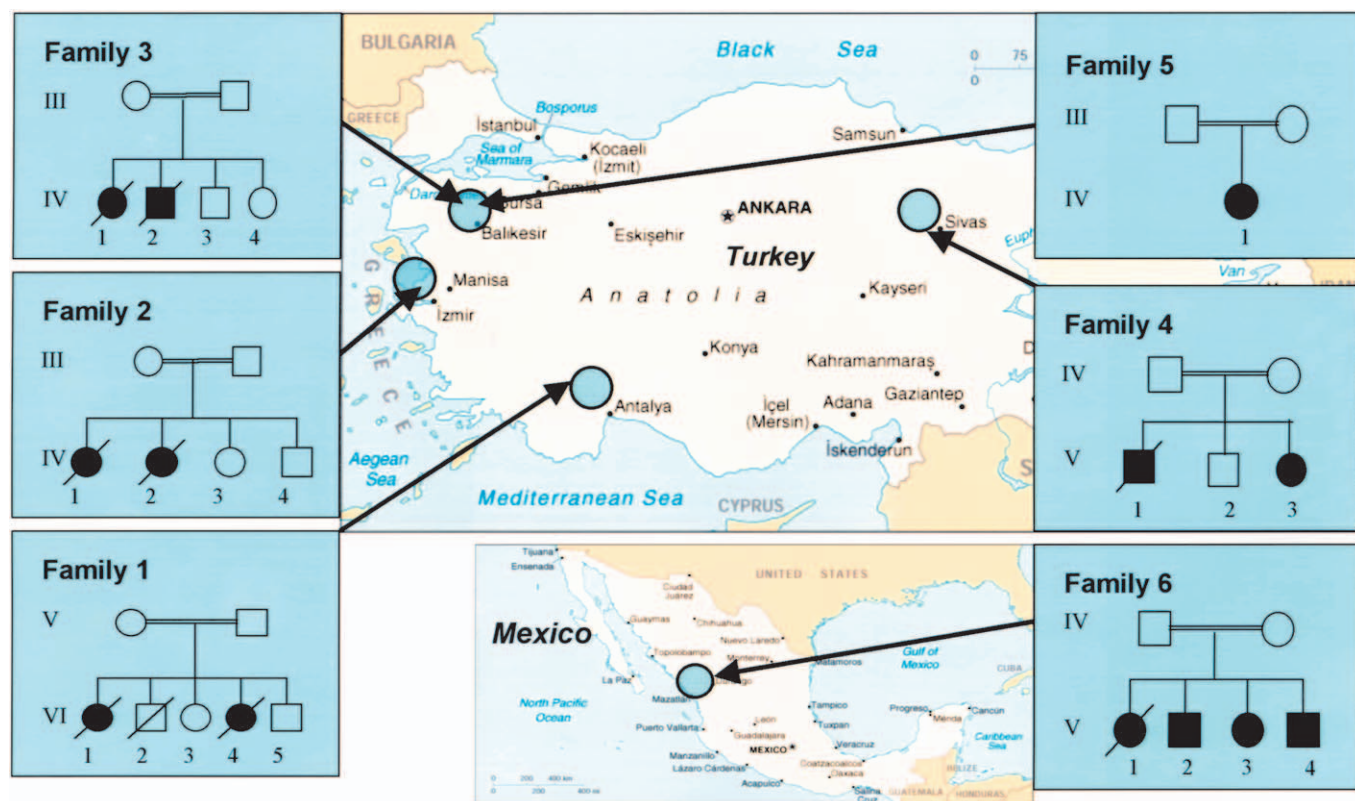


Fig 1. Partial pedigrees and origin of six consanguineous families with AR-HIES. See online version for extended pedigrees illustrating consanguineous relationships. *Filled symbol*, affected subject; *open symbol*, unaffected subject; *slash*, deceased.

inheritance have been reported.^{2,7,13-15} Recent evaluation of 30 patients with HIES and 70 of their relatives showed that HIES can be inherited as a single-locus autosomal-dominant trait with variable expressivity (AD-HIES), and that in some families, HIES is linked to markers on chromosome 4.^{2,15}

We describe 13 patients from six consanguineous families in which HIES was inherited in a manner more consistent with autosomal-recessive inheritance (AR-HIES). We show that AR-HIES is a clinically distinct disease.

METHODS

In six consanguineous families (Fig 1), 13 patients were suspected of having a primary immunodeficiency based on unusual, severe, recurrent infections (Table I) and eczematoid rashes. Laboratory screening demonstrated elevated serum IgE levels and pronounced eosinophilia (Table I). All patients >1 year old fulfilled the clinical triad of HIES consisting of recurrent skin abscesses, recurrent pneumonia, and elevated IgE levels. Detailed case reports of the families are published in the online version of this article. The single child in family 5 could also be a sporadic case of HIES. However, she was included in our analysis because the family was consanguineous, came from the same region of Turkey as two other families, and had a phenotype similar to that of our other patients. These patients and 68 of their relatives were evaluated with informed consent under approved protocols at the Charité University Children's Hospital, Berlin (families 1 and 4), the

Dr. von Haunersches Children's Hospital, Munich (families 2-5), the University Children's Hospital, Münster (family 5), and the Warren Grant Magnuson Clinical Center, National Institutes of Health, Bethesda (family 6). All subjects had a complete history and review of previous records. Physical examination with anthropometric measurements and laboratory investigations were performed on all living patients and their first-degree relatives. Levels of IgG, IgA, IgM, IgE, and IgG subclasses; specific antibody titers against cytomegalovirus, herpes simplex virus, diphtheria, and tetanus; and hemolytic complement levels were determined for most patients. Lymphocyte cell surface marker expression was analyzed with a three-color FACScan (Beckton Dickinson, San Jose, Calif) and the StimulTest IMK Plus (Beckton Dickinson). Lymphocyte stimulation on four patients was performed at the Laboratory of Immunology, Dr. v. Haunersches Kinderspital, by using a standard protocol.¹⁶ For family 5, person IV.1, the lymphocyte stimulation tests were performed at the University of Zürich by using the antigens *Candida*, diphtheria, tetanus, and purified protein derivative of tuberculin. Granulocyte chemotaxis was assayed with the under agarose technique.¹⁷ Nitroblue-tetrazolium reduction was performed according to a standard protocol.¹⁸

An HIES scoring system,¹⁵ developed at the National Institutes of Health to phenotype patients with AD-HIES and their relatives, was applied to available members of the six families enrolled in this study. In brief, patients were evaluated for the existence and severity of the following 20 clinical and laboratory features: newborn rash, eczema, skin abscesses,

Table I. Clinical and laboratory findings in 13 consanguineous patients with AR-HIES

Patient	Age	Sex	Serum IgE peak, IU/mL (normal <130)	Eosinophils/ μ L (normal <700)	No. of documented pneumonias	Recurrent viral infections	National Institutes of Health HIES score [†]
Family 1, VI.4	12½ y*	Female	45,100	7072	7	HSV, VZV	52
Family 1, VI.1	2 y*	Female	1992	17,874	2	HSV	≥50 [§]
Family 2, IV.2	2 y*	Female	1693	4984	3	HSV	≥48 [§]
Family 2, IV.1	6 mo*	Female	NA	NA	2	NA	≥23 [§]
Family 3, IV.1	8¾ y*	Female	23,000	9810	4	HSV, VZV	48
Family 3, IV.2	11 mo*	Male	Elevated [‡]	NA	NA	None	≥15 [§]
Family 4, V.3	8 y	Female	19,350	4550	12	HSV, M contagiosum	36
Family 4, V.1	3½ y*	Male	4510	12,390	1	HSV	≥45 [§]
Family 5, IV.1	10 y	Female	38,454	16,259	5	M contagiosum	48
Family 6, V.1	1 y*	Female	NA	NA	1	None	≥19 [§]
Family 6, V.2	16 y	Male	5992	13,600	2	None	45
Family 6, V.3	10 y	Female	39,669	4730	2	HSV, M contagiosum	53
Family 6, V.4	8 y	Male	31,348	2610	2	HSV, M contagiosum	42

HSV, Herpes simplex virus; NA, Data not available; VZV, Varicella-zoster virus.

*Age at death.

†See Grimbacher et al.¹⁵

‡Parents' information.

§Based on incomplete evaluation; additional features of HIES may have been present.

recurrent upper respiratory infections, pneumonia, parenchymal lung changes, candidiasis, other severe infections, fatal infections, characteristic facies, increased interalar distance, high palate, retained primary dentition, hyperextensibility, pathologic fractures, scoliosis, midline anomalies, lymphoma, high serum IgE level, and eosinophilia. An age correction was introduced to compensate for the occurrence of fewer abnormalities at young ages.

RESULTS

Genetics

The pedigrees of the six consanguineous families with AR-HIES are depicted in Figure 1. Four male and nine female patients were offspring of consanguineous matings; affected subjects were seen in only one generation of each family. Thus, the inheritance pattern is most consistent with an autosomal-recessive mode. Though not known to be related to each other, five families were from Turkey. Therefore, the origin of these families is of genetic interest. Figure 1 shows that families 2, 3, and 5 were from the west coast of Turkey, family 1 from the south, and family 4 from central Turkey. The latter two were separated from the others by a distance of more than 300 km. Family 6 was of Mexican descent.

At diagnosis, patients were between 6 months and 5 years old. Subsequently, eight patients have died at ages ranging from 6 months to 12 years.

In AD-HIES families, an HIES genotype was considered highly likely if the HIES score (based on numbers and severity of HIES characteristics exhibited) exceeded 40 points

and possible if the score exceeded 20 points.¹⁵ The scores of patients with AR-HIES >1 year old ranged from 36 to 53 (Table I). In all but two patients, features contributing to these scores were from infectious and immunologic conditions, notably eczema, abscesses, frequent respiratory infections, and candidiasis. All 68 relatives had less than 20 points, suggesting that they were unlikely to be affected by HIES, further supporting an autosomal-recessive trait.

Dental and Skeletal Abnormalities

Failure or delay of shedding of the primary teeth because of the lack of tooth root resorption is a specific feature of AD-HIES^{2,12} but was not documented in the AR-HIES cohort. Five subjects with AR-HIES had normal dental development, two required primary tooth extractions because of severe caries, and six patients' dental status could not be assessed because of early death or evaluation <4 years of age.

Pathologic fractures, scoliosis, and hyperextensible joints are frequent nonimmunologic findings in AD-HIES.² There were no fractures in the cohort of patients with AR-HIES. One patient developed scoliosis, which may have been secondary to spasticity of all extremities. In one patient with AR-HIES, mild hyperextensibility was documented.

Patients with AR-HIES had no facial phenotype. Seven patients with AR-HIES were >8 years old, and one of them was >16 years old, an age at which the characteristic wide nose, deep-set eyes, prominent chin and forehead, and thickened skin are present in AD-HIES. Pictures of the deceased persons were also reviewed, and they did not show characteristic facies.

Infections and Immunologic Features

All but two patients with AR-HIES, who died during the first year of life, fulfilled the clinical triad of recurrent skin abscesses, recurrent pneumonia, and elevated serum IgE level (Table I). Severe eczematoid rashes were a universal finding. In three patients, eczema occurred within the first 6 weeks of life; the others developed severe eczema by age 3 years. All affected patients had more than four clinically documented upper respiratory infections per year, including bronchitis, otitis, and sinusitis. Respiratory infections in patients with AR-HIES were caused by *Staphylococcus aureus*, *Haemophilus influenzae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Cryptococcus neoformans*.

Pleural effusion or empyema often accompanied pneumonia. Although in AD-HIES, pneumonias tend to form lung abscesses and pneumatoceles, these did not occur in the 13 patients with AR-HIES.

As with skin abscesses in other patients with HIES, those in AR-HIES were most frequently caused by *S aureus*. Other bacterial infections in patients with AR-HIES included fatal sepsis caused by *S aureus*, *Escherichia coli*, or *Enterococcus faecalis*. Similarly, fungal infections were a major cause of morbidity in AR-HIES. Chronic candidiasis of mucosal sites was documented in 10 of the 13 patients with AR-HIES, with nail bed involvement in seven.

Chronic, disfiguring molluscum contagiosum infection, located on the umbilicus, face, and genital region, was seen in four patients with AR-HIES and did not respond to therapy. This infection is not typical for AD-HIES. In our AR-HIES cohort, seven patients had recurrent herpes simplex infections leading to aphthous stomatitis and keratitis, and one patient had recurrent varicella-zoster infection of the facial and thoracic nerves, demonstrating an increased severity and defective control of viral infections.

Parasitic infections were never diagnosed in patients with AR-HIES despite repeated stool examinations. Allergic bronchopulmonary aspergillosis has also not been documented. At least one patient per family was shown to be HIV-seronegative.

High levels of IgE and eosinophilia were persistent in all patients with AR-HIES; the highest documented values for IgE and eosinophils are listed in Table I. The extent of the IgE elevation in AR-HIES is comparable with that seen in AD-HIES.² However, the patients with AR-HIES had significantly higher eosinophil counts when compared with the large cohort of sporadic HIES and AD-HIES cases published by Grimbacher et al ($P < .005$, two-sided t test).²

Radioallergosorbent tests were performed in six of 13 patients; however, no uniform pattern was detected. As example, patient VI.4 from family 1 showed high specific IgE titers to almost all antigens tested, whereas patient IV.1 from family 5 did not have any IgE antibodies against common allergens. However, RAST data in patients with IgE serum levels this high are of questionable value. Because of ongoing eczema, skin testing in the patients was not performed or could not be interpreted.

Two patients had recurrent autoimmune hemolytic anemia (family 1, VI.4, and family 3, IV.1); the patient from

family 3 also had a pericardial effusion that may have been of autoimmune origin.

Lymphocyte cell surface phenotyping was performed in the six index patients with AR-HIES, and in vitro lymphocytic proliferation assays were performed in the five Turkish index patients, as listed in Table II. Although no major abnormality in the number or distribution of the lymphocyte subpopulations was observed, two of six patients had low total T-cell counts; however, the CD4:CD8 ratio was normal in these patients. The NK-cell and the B-cell compartments appeared normal, with the exception of a low B-cell count in the patient of family 2. In addition to the known extreme elevation of IgE, the levels of other antibody isotypes were often elevated, consistent with a general stimulation of the humoral immune system.

On stimulation with mitogens, lymphocyte proliferation after 3 days was reduced in three patients, and a normal response was documented in two. This finding may indicate a qualitative T-cell defect. Furthermore, all patients tested had severely reduced proliferation in response to staphylococcal antigen Cowan strain I (a T-cell-independent B-cell mitogen) and to soluble recall antigens after 7 days of culture. These findings suggest impairments of the humoral and cellular immune systems in AR-HIES.

Granulocyte function, as assessed by chemotaxis and nitroblue-tetrazolium reduction, was not significantly impaired in our cohort of patients with AR-HIES.

Central Nervous System Disease and Neurologic Symptoms

In the AR-HIES cohort, seven of 13 patients had neurologic symptoms ranging from hemiplegia to paralysis of the facial nerve (see Case Report with alternative Figure 2a in the online version of this article, www.us.elsevierhealth.com/jpeds). Of those seven patients, four died, documenting the severity of this complication. In two of the four deceased, autopsies were performed. A ruptured cerebral aneurysm was found in one (family 3, IV.1) and a severe necrotizing encephalitis of the gray matter with reactive sclerosis of the astroglia in the other (family 4, V.1; Fig 2). In both histologies, a lymphocytic but not eosinophilic infiltrate (as would be expected for an eosinophilic vasculitis) was found; however, no pathogen was identified.

The third patient (family 1, VI.4) was radiologically well studied (Fig 2) and had two cerebral strokes. The first may have been induced by an embolic event, because a hyaline membrane was identified in the cardiac left atrium. However, during the second attack, an angiogram showed inconsistencies in caliber of the basal cerebral arteries. These changes are seen in vasculitis of the large and medium-sized arteries, or in infections such as mycoses or syphilis. The small vessels, frequently affected in isolated vasculitis of the central nervous system (CNS), were normal in these patients with AR-HIES.

In the fourth case (family 2, IV.2), fatality was associated with sepsis, leukocytoclastic vasculitis, and retinal hemorrhages. The computed tomography (CT) scan before death showed a subarachnoid hemorrhage and edema.

Table II. Immunologic tests from the index patients of each family with AR-HIES

Patient	Family 1, VI.4	Family 2, IV.2	Family 3, IV.1	Family 4, V.3	Family 5, IV.1	Family 6, V.3
Test, patient characteristic						
Age at test	7 y	15 mo	7 y	5 y	5 y	10 y
Health status at test	No acute infection	No acute infection	No acute infection	No acute infection	No acute infection	No acute infection
Total lymphocytes cells/ μ L	3088 (1000–5900)	4752 (2700–11,900)	1134 (1100–5900)	3234 (1100–5900)	1540 (1100–5900)	2691 (1000–5300)
CD3+, cells/ μ L	2038 (700–4200)	2471 (1400–8000)	646 L (700–4200)	1681 (700–4200)	820 (700–4200)	606 L (800–3500)
CD4+, cells/ μ L	772 (300–2000)	1616 (900–5500)	227 L (300–2000)	1358 (300–2000)	420 (300–2000)	412 (400–2100)
CD8+, cells/ μ L	1112 (300–1800)	998 (400–2300)	386 (300–1800)	420 (300–1800)	350 (300–1800)	178 L (200–1200)
CD4: CD8 ratio	.7 L (.9–2.6)	1.6 (.9–3.7)	1.7 (.9–2.6)	3.2 H (.9–2.6)	1.2 (.9–2.6)	2.31 (.9–3.4)
CD3-16+/56+, cells/ μ L	278 (90–900)	523 (100–1450)	ND	291 (90–900)	280 (90–900)	103 (70–1200)
CD19+ or CD20+, cells/ μ L	803 (200–1600)	238 L (600–3100)	238 (200–1600)	1034 (200–1600)	510 (200–1600)	564 (200–600)
IgG, mg/dL	1120 (590–1500)	1140 (360–1230)	1970 H (590–1500)	1280 (540–1430)	1450 H (540–1430)	1800 H (670–1530)
IgG subclasses	No deficiency	No deficiency	No deficiency	No deficiency	No deficiency	ND
IgA, mg/dL	420 H (30–222)	437 H (37–156)	102 (30–222)	81 (30–222)	220 (30–222)	377 H (52–274)
IgM, mg/dL	360 H (52–208)	64 (40–175)	297 H (52–208)	93 (52–208)	127 (52–208)	84 (48–179)
Specific IgG	Positive for CMV, HSV, EBV, VZV	Positive for HSV, CMV, VZV, EBV	Positive for measles, EBV, CMV, HSV	Positive for HSV Diphtheria, Tetanus	Positive for tetanus, CMV, diphtheria, <i>Candida</i>	ND
Lymphocyte proliferation*						
PHA, cpm	ND	36,044 (67,056)	10,002 (57,916)	77,933 (86,970)	83,875 (83,589)	ND
OKT 3, cpm	Reduced [†]	20,496 (53,986)	ND	67,583 (70,673)	73,265 (132,914)	ND
Con A, cpm	ND	12,563 (36,298)	3542 (47,361)	40,948 (48,318)	ND	ND
PWM, cpm	ND	10,194 (28,897)	6205 (20,588)	30,184 (18,250)	23,619 (47,704)	ND
SAC, cpm	ND	1019 L (15,688)	ND	1547 L (5262)	ND	ND
Antigen mixture, cpm	Reduced [†]	1195 L (57,712)	232 L (53,853)	7754 L (77,083)	ND	ND
<i>Candida</i> , cpm	ND	ND	ND	ND	4694 L (23,301)	ND
Diphtheria, cpm	ND	ND	ND	ND	5690 L (17,883)	ND
Tetanus, cpm	ND	ND	ND	ND	3951 L (16,167)	ND
PPD (tuberculin), cpm	ND	ND	ND	ND	2975 L (7545)	ND
Granulocyte diagnostics*						
Nitroblue-tetrazolium test	Reduced ^{†‡}	100% (100%)	100% (100%)	Uninterpretable [§]	Normal [†]	ND
Chemotaxis [mm/2 h]	Normal ^{†‡}	4.6 (6.5)	7.7 (9.2)	5.1 (7.5)	.69 (1.73)	ND

H, Value elevated^{25,26}; L, value reduced^{25,26}; HSV, herpes simplex virus; VZV, Varicella-zoster virus; ND, not done; CMV, cytomegalovirus; Con A, conavalin A; cpm, counts per minute; EBV, Epstein-Barr virus; PHA, phytohemagglutinin; PPD, purified protein derivative of tuberculin; PWM, pokeweed mitogen; SAC, staphylococcal antigen Cowan strain I.

*Values of a healthy control are shown in parentheses.

[†]Exact laboratory value not available.

[‡]Test at 5 years of age.

[§]As a result of hyper eosinophilia (24%).

Three patients with AR-HIES with neurologic symptoms are still alive. One patient's complex neurologic deficit can be attributed to the sequelae of a cryptococcal meningitis (family 6, V.3), and one patient's peripheral facial nerve palsy followed a bout of otitis media (family 5, IV.1). The third patient had hemiplegia (family 4, V.3), with a CT scan showing multiple hypodensities with perifocal edema and angiography revealing underperfusion of the large arteries and occlusion of small vessels. Cerebrospinal fluid and serology were negative. She improved after receiving antibiotics, acyclovir, and steroids.

Taken together, in a total of five of the seven patients with neurological symptoms documented vascular anomalies

(ie, stenosis, occlusion, and aneurysm formation) led to cerebral infarction, subarachnoid hemorrhages, or both. In three of the seven, an infectious cause (sepsis, cryptococcal meningitis, otitis) was a possible factor underlying the neurologic disease.

DISCUSSION

We have defined a novel autosomal-recessive variant of HIES. AR-HIES can be separated from AD-HIES by four major criteria, and therefore represents a distinct disease entity. First, the inheritance pattern of HIES in the six consanguineous families is very likely to be autosomal-recessive. Second, AR-HIES has no connective tissue features. AR-HIES appears to be limited to immune and

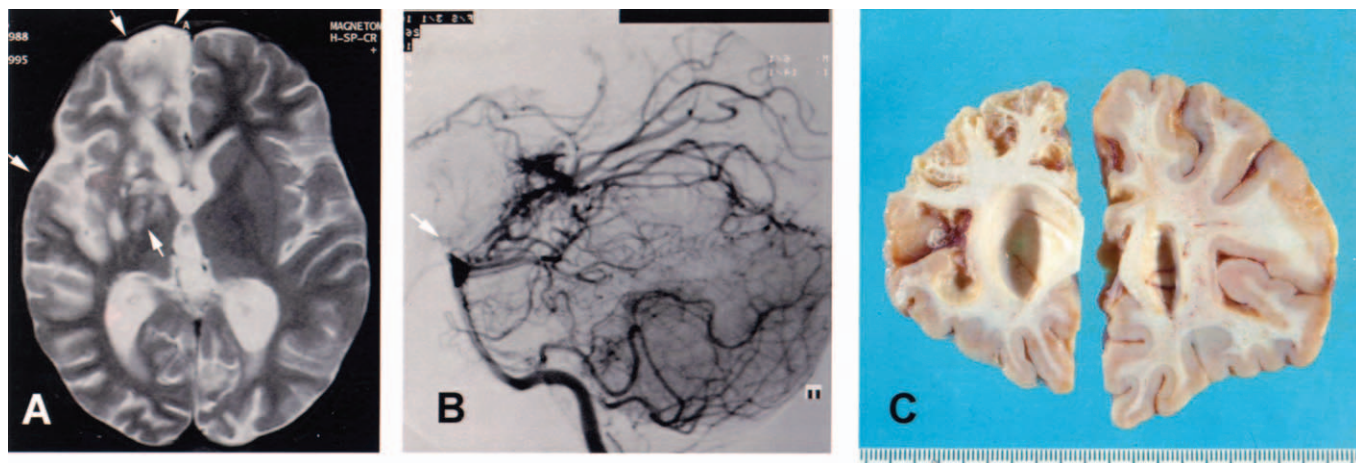


Fig 2. Central nervous system findings in patients with AR-HIES. **A**, Brain MRI in patient VI.4 (family 1) showing extensive cortical necrosis of the right frontal hemisphere, basal ganglia, and putamen. **B**, Angiography from the same patient performed the same day as the MRI, showing complete occlusion of the right anterior and middle cerebral arteries. The basilar arteries show segmental dilatation and stenosis. No embolus or atherosclerotic changes are seen. **C**, Autopsy of patient V.1 (family 4) showing extensive microcystic necrosis of the gray matter of the left hemisphere with involvement of the putamen. Frontal cortex is relatively spared, and basal ganglia and right hemisphere are uninvolved (as are cerebellum and brain stem, not shown).

inflammatory abnormalities. Third, AR-HIES has a particularly high incidence of CNS complications, with devastating and fatal outcome. Fourth, the types of infections and immunologic features in the variants of HIES differ. Patients with AR-HIES can develop severe infection with molluscum contagiosum, which we have not encountered in patients with sporadic HIES or AD-HIES. However, Martins et al¹⁹ recently described one patient with sporadic HIES and severe molluscum contagiosum infection. Moreover, in AR-HIES, there seems to be a higher frequency and younger age of complications from varicella-zoster and herpes simplex viruses. Furthermore, pneumatocele formation after pneumonia, typical for AD-HIES, has not been documented in AR-HIES, despite a similar frequency of pneumonias (≥ 42 episodes in 13 patients with AR-HIES and 83 patient-years). In addition, the level of eosinophilia is significantly higher in AR-HIES compared with AD-HIES.

Elevated IgE and eosinophilia are seen in atopic dermatitis and primary immunodeficiencies including the Wiskott-Aldrich syndrome, Omenn syndrome, and the Netherton-Comèl syndrome.¹ However, the phenotype of AR-HIES clearly differs from those entities. Eosinophilia is the hallmark of the hypereosinophilic syndrome, characterized by eosinophil counts greater than $1.5 \times 10^3/\mu\text{L}$ persisting for at least 6 months and leading to organ damage.²⁰ CNS disease such as ischemic infarction caused by thrombosis is present in 58% of the patients with the hypereosinophilic syndrome, and anemia is reported in 50%.²⁰ In 10 of our 13 patients with AR-HIES, eosinophilia was marked and persistent. Moreover, five of the 10 presented with vascular disease of the CNS, and two had recurrent hemolytic anemia, also seen in the hypereosinophilic syndrome. Therefore, the phenotype of AR-HIES overlaps with HIES and hypereosinophilic syndrome.

Central nervous system involvement may occur in AD-HIES², however, in currently published series, it is not frequent. In contrast, devastating neurological manifestations

were present in seven of our 13 patients with AR-HIES. Although two autopsies and multiple CT scans, magnetic resonance imaging (MRI) scans, and angiograms were performed, the cause of this complication remains unclear. In the first patient, brain examination post mortem demonstrated a ruptured aneurysm, suggesting that inflammatory aneurysms could underlie episodes of intracranial hemorrhage. In the second patient, widely distributed microcystic lesions in the grey matter of the left hemisphere argue against occlusion of a major vessel as the primary cause. However, in neither case was any evidence of bacterial, fungal, or viral pathogen detected. A third patient was diagnosed with cryptococcal meningitis, and a fourth with a hyaline membrane in the left atrium, which may have been the source of a cerebral embolic stroke. However, the second stroke in this patient and similar events in three other patients remain unexplained. Although cerebral masses, coagulation disorders, and valvular vegetations were excluded in all instances, eosinophilia, autoimmune disease, or infection may have contributed to these vascular injuries. Although the precise causes of brain vascular injury are not clear, the incidence of this complication in AR-HIES is high; six of the seven patients who had MRI studies had vascular abnormalities (only patient IV.1 from family 5 had a normal MRI scan).

The occurrence of hemolytic anemia in two of our patients with AR-HIES suggested autoimmunity. In one patient, antinuclear antibodies were detected, whereas ds-DNA antibodies were negative; the other patient had, in addition to hemolytic anemia, a pericardial effusion with a suspected autoimmune cause. Autoimmunity and immune dysregulation are well recognized in many primary immunodeficiencies, including autoimmune lymphoproliferative syndrome, autoimmune polyendocrinopathy-candidiasis-ectodermal-dystrophy (APECED), and common variable immunodeficiency.²¹ Two patients with HIES followed at the National Institutes of Health have had idiopathic thrombo-

cytopenia, known to be associated with autoantibodies against platelets. Moreover, systemic lupus erythematosus has been reported in patients with HIES.²² Thus, autoimmune disease is observed in all forms of HIES but may be more frequent in AR-HIES.

Lymphocyte proliferation tests of patients with HIES demonstrated defective responses to SAC and antigen stimulation and suggested reduced mitogen responses in some patients. However, because proliferation to specific antigens in vitro is linked to previous host encounter with those antigens, these data must be interpreted cautiously. Nonetheless, the patient in family 5 had recurrent candidiasis, but her lymphocytes still failed to proliferate to *Candida* antigen. Explanations for poor in vitro responses include ineffective antigen presentation to T cells, reduced ability to generate antigen-specific T cells, or increased T-suppressor activity resulting in a state of anergy. The ongoing molluscum infections in four patients were not associated with any consistent abnormality in lymphocyte subsets. More thorough studies of the T-cell and B-cell compartments in these patients, including assessment of cytokine production and the lymphocyte signaling, are warranted and may provide insight into the mechanisms involved in AR-HIES. Recent studies with patients with sporadic HIES indicated that cytokines and chemokines may be dysregulated in HIES, although it is not clear whether these abnormalities are primary or secondary to intercurrent infection and inflammation.^{23,24}

Our patients were children of consanguineous matings. Thus, an autosomal-recessive trait is highly likely. Five of the families originate from Turkey, so the possibility of a common founder is suggested (Fig 1). Families 2, 3, and 5 are from the same region. For AD-HIES, a disease locus for some families has been identified on chromosome 4 by linkage analysis.¹⁵ Preliminary assessment of chromosome 4 genotypes in the consanguineous families reported here did not show linkage of AR-HIES to chromosome 4q21 (data not shown).

Although fulfilling the clinical triad for HIES with recurrent staphylococcal infections of the skin and lungs and elevated serum IgE, patients with AR-HIES had a distinctive immunologic and infectious phenotype and lacked the skeletal or dental abnormalities seen in AD-HIES. AR-HIES is distinguished by a striking vasculitis of the CNS, increased susceptibility to intractable viral infections, and autoimmune complications more frequent than in sporadic HIES or AD-HIES. Thus, AR-HIES represents a previously unrecognized, distinct disease that may be genotypically unrelated to AD-HIES.

We thank Dr M. Uhl for review and interpretation of radiographic data and Dr M. Schlesier for interpretation of immunologic data.

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