

ORIGINAL ARTICLE

The clinical and laboratory survey of Iranian patients with Hyper-IgE syndrome

MOSTAFA MOIN¹, ABOLHASSAN FARHOUDI¹, MASOUD MOVAHEDI¹,
NIMA REZAEI¹, ZAHRA POURPAK¹, MEHDI YEGANEH¹,
MOHAMMAD GHARAGOZLOU¹, BAHRAM MIRSAEID GHAZI¹, SABA ARSHI²,
DAVOUD MANSOURI³, ROYA SHERKAT⁴, SARA KASHEF⁵, MARYAM MAHMOUDI¹,
MOHAMMAD NABAVI^{1,5} & ASGHAR AGHAMOHAMMADI¹

From the ¹Department of Allergy and Clinical Immunology of Children Medical Centre, Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, ²Rasoul Akram Hospital, Iran University of Medical Sciences, Tehran, ³Department of Infectious Diseases, Masih Daneshvari Hospital, Shaheed Beheshti University of Medical Sciences, Tehran, ⁴Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, and ⁵Department of Immunology and Allergy, Shiraz University of Medical Sciences, Namazi Hospital, Shiraz, Iran

Abstract

In order to determine the clinical and laboratory findings of Iranian patients with presumed hyper-immunoglobulin E syndrome (HIES), the medical records of 22 patients from 21 unrelated families, who had been registered in the Iranian Primary Immunodeficiency Registry, were observed. The median age of patients at the time of first symptom and at the time of diagnosis was 1 month and 52.5 months, respectively, with a median diagnosis delay of 70 months. 13 families had consanguineous marriages. IgE level was higher than 2000 IU/ml in all patients, ranging from >2000 to 80,000 IU/ml. The most commonly occurring manifestations were: eczema and dermatitis, pneumonia, upper respiratory tract infections, cutaneous abscesses, diarrhoea, deep abscesses, and otitis media. Other less frequent manifestations were: mucocutaneous candidiasis, sinusitis, cutaneous ulcers, Molluscum contagiosum, herpetic keratitis, onychomycosis, conjunctivitis, septic arthritis, and meningitis. Five patients were complicated by bronchiectasis due to recurrent pneumonia and 5 patients died because of severe infections and malignancy. The HIES is a multisystem disorder that affects especially cutaneous, respiratory, skeletal and the immune system. Although HIES is a rare condition, the recurrent infections should always raise a suspicion, which deserves further evaluation for detecting the syndrome.

Introduction

The hyper-immunoglobulin E syndrome [HIES; Online Mendelian Inheritance in Man (OMIM) #147060], also known as Job syndrome (OMIM #243700), is a very rare primary immunodeficiency disorder (PID), characterized by the clinical triad of recurrent staphylococcal skin abscesses, recurrent cyst-forming pneumonia, and high serum levels of immunoglobulin E (IgE > 2000 IU/ml) [1–5]. It is a multisystem disorder of unknown cause that affects the immune system, skeleton, connective tissue, and dentition [1,4]. There is a marked variation in the constellation

of symptoms and signs that constitute the diagnosis [3–9].

Most cases of HIES are sporadic; however, multiplex families displaying autosomal dominant (AD) and autosomal recessive (AR) inheritance have been described [1,4,8,10–13]. HIES occurs in individuals from diverse ethnic backgrounds and does not seem to be more common in specific populations [4].

The purpose of the present study is to determine the spectrum of clinical and immunological features of Iranian patients with HIES, referred to the main immunodeficiency referral center in Iran [14,15].

Correspondence: M. Moin, Immunology, Asthma and Allergy Research Institute, Children Medical Centre, P.O.Box: 14185-863, No. 62, Dr. Gharib St., Keshavarz Blvd., Tehran 14194, Iran. Tel: +98 21 6693 58 55. Fax: +98 21 6642 89 95. E-mail: rezaei_nima@hbi.ir and mmoin@sina.tums.ac.ir

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Material and Methods

Medical records of 22 patients from 21 unrelated families with the diagnosis of HIES were reviewed for this report. The patients were registered at the Iranian Primary Immunodeficiency Registry (IPIDR) [14,15]. Data was gathered by interviewing patients and their families, as well as reviewing medical records of a 25-year period (1980–2005). For all subjects, we took a complete medical history, reviewed medical documents, performed physical examinations, and conducted laboratory studies. An HIES scoring system developed at the National Institutes of Health, was applied to the patients enrolled in this report (10). In brief, patients were evaluated for the existence and severity of the following 20 clinical and laboratory features: newborn rash, eczema, skin abscesses, recurrent upper respiratory infections, pneumonia, parenchymal lung changes, candidiasis, other severe infections, fatal infections, characteristic facies, increased inter-alar distance, high palate, retained primary dentition, hyperextensibility, pathologic fractures, scoliosis, midline anomalies, lymphoma, high serum IgE level, and eosinophilia. All patients had a total-point score greater than 15 (Table I). Data analysis was performed using SPSS statistical software package, version 11.0 (SPSS Inc, Chicago, IL).

Results

Characteristics of Patients

Twenty-two HIES patients (11 males and 11 females) with a mean age of 15.4 ± 5.7 years were reviewed. The first infectious manifestation had occurred at a median age of 1 month (range: 1 month–3 years). Fifteen cases experienced symptoms by the age of 1 month, while 3 patients did not experience any symptoms until the age of 1 year (Table I). The median age of patients at the time of diagnosis was 52.5 months (range: 13 months–14 years; mean: 80.5 ± 50.5 months), with a median diagnosis delay of 70 months (range: 1–13 years; mean: 75.3 ± 48.5 months). Although half of the patients were diagnosed before the age of 4 years, five patients were not diagnosed until the second decade of their life.

Consanguinity and Family History

In 13 families, parents were consanguine, including first cousins (ten families), second cousins (one family), and beyond second cousins (two families). A history of recurrent infections in siblings of the affected member was found in nine families

(40.9%); however, we found only one family with two affected members (P9 and P18) (Table I).

Humoral Immunity

Laboratory analysis revealed an IgE serum level higher than 2,000 IU/ml in all patients, ranging from >2,000 to 80,000 IU/ml. Eosinophilia has been detected in 18 patients (81.8%). The median absolute number of eosinophils was $892.2/\mu\text{l}$ (range: 110–15,834/ μl) and the percentage of eosinophils varied from 2% to 60% (Table II). At the time of diagnosis, the median serum levels for IgG was 1,970 mg/dl (1,050–3,000 mg/dl), for IgA 137.5 mg/dl (75–928 mg/dl) and for IgM 160 mg/dl (35–340 mg/dl) (Table II).

Cellular Immunity

Total white blood cell (WBC) counts ranged from normal to markedly elevated ($27,300/\mu\text{l}$) in patients with acute infections. None of our patients was neutropenic or lymphopenic, but four patients had anemia. Almost all of patients had normal counts of CD3+, CD4+, CD8+, and CD19+ lymphocytes; In immunophenotyping, the median number of CD3+ T-cells were 635 cells/ μl , CD4+ T-cells were 328.2 cells/ μl , CD8+ T-cells were 228.5 cells/ μl , and CD19+ B-cell number was 219.5 cells/ μl . A reduced peripheral B lymphocyte count was found in one patient (P2), and low counts of T lymphocytes were identified in four patients (P4, P15, P19, and P21) (Table II).

Presenting Illness

The most common presenting feature of HIES was a neonatal rash, which was seen in 18 patients. Other presenting manifestations were: cutaneous abscesses (three patients), lung abscesses (two patients), pneumonia (two patients), otitis media (one patient), and diarrhea (one patient).

Infections during the Course of Disease

Acute and recurrent infections were found in almost all of our patients, particularly involving the respiratory system. The most common occurring infections (in descending order of frequency) were: pneumonia (17 cases), upper respiratory tract infections (15 cases), skin abscesses (15 cases), diarrhea (12 cases), deep-seated abscesses (11 cases), and otitis media (11 cases). Abscesses have been detected as one of the frequent manifestations of patients, affecting different organs, including: skin (15 cases), lung (four cases), liver (two cases), genitalia (two

Table I. Characteristics of Iranian patients with Hyper-IgE Syndrome.

Patient No.	Sex	Age of study (years)	Age of onset (months)	Diagnosis age (months)	Consanguinity	Family history of recurrent infections	HIES Score
P1	Male	28	1	96	No	No	41
P2	Female	24	1	36	Yes	No	37
P3	Female	23	1	19	No	Yes	48
P4	Female	21	1	43	Yes	No	32
P5	Male	19	1	86	No	No	27
P6	Male	18	1	96	No	No	35
P7	Male	18	1	13	No	No	42
P8	Male	18	1	20	Yes	No	37
P9	Female	17	12	168	Yes	Yes (Sister of P18)	34
P10	Male	16	1	48	Yes	No	31
P11	Male	8	1	48	No	No	26
P12	Female	16	1	154	No	No	21
P13	Female	12	1	48	Yes	No	39
P14	Male	11	24	108	Yes	Yes	34
P15	Female	15	36	132	Yes	Yes	38
P16	Female	13	1	57	No	Yes	34
P17	Female	13	4	132	Yes	No	33
P18	Male	14	6	140	Yes	Yes (Brother of P9)	33
P19	Female	13	36	48	Yes	Yes	27
P20	Male	11	1	108	No	Yes	33
P21	Male	8	1	41	Yes	Yes	30
P22	Female	3	3	15	Yes	No	44

cases), brain (one case), and bone (one case). Other less frequent manifestations were: sinusitis (eight cases), cutaneous ulcers (six cases), conjunctivitis (four cases), septic arthritis (three cases), and meningitis (one case). In five patients the course of the disease was complicated by bronchiectasis due to

recurrent pneumonia. It is notable that skin abscesses were reported only in two third of our patients, which is much lower than previous cohorts [1,2,9,16,17]. Mucocutaneous candidiasis was also found in nine (40%) of our patients, which is much lower than previous studies [1,4,8,16,17].

Table II. Laboratory findings of patients with Hyper-IgE Syndrome.

Patient No.	Serum IgG (mg/dl)	Serum IgM (mg/dl)	Serum IgA (mg/dl)	Serum IgE (IU/ml)	Eosinophil percentage	Absolute number of Eosinophils (cells/mm ³)	Number of T-cell CD3+	Number of T-cell CD4+	Number of T-cell CD8+	Number of B-cell CD19+
P1	2800	280	440	3300	14.6%	934.40	632	—	—	—
P2	1200	160	236	10000	16.0%	1072.00	2296	1665	760	137
P3	1540	204	156	80000	7.0%	980.00	2994	1959	947	933
P4	1050	102	100	2100	5.0%	590.00	2124	—	—	850
P5	1150	90	94	>2000	7.0%	721.00	1784	845	840	643
P6	—	—	—	>2000	10.0%	850.00	—	—	—	—
P7	2600	120	390	5000	15.0%	1770.00	3018	1217	1588	447
P8	1350	168	127	5600	16.5%	712.80	574	436	162	234
P9	—	—	—	>2000	33.0%	4917.00	—	—	—	—
P10	2500	160	80	5000	2.7%	665.80	—	—	—	—
P11	3000	280	84	>2000	5.0%	110.00	—	—	—	—
P12	1600	168	148	>2000	10.0%	750.00	—	—	—	—
P13	2440	294	94	2500	14.2%	708.58	1172	837	381	434
P14	2440	146	928	2070	5.8%	768.50	1733	625	582	231
P15	2250	198	2252	2450	58.0%	15834.00	687	—	—	412
P16	1900	340	120	5000	29.0%	6786.00	2799	1676	710	1517
P17	2180	50	75	>2000	60.0%	12720.00	1011	477	475	181
P18	—	35	170	>2000	26.0%	4238.00	719	639	205	319
P19	—	—	—	2291	11.0%	781.00	286	135	—	—
P20	1250	115	105	3000	2.0%	234.00	3489	1867	1278	1278
P21	1970	52	355	>2000	24.0%	3168.00	1615	666	1373	1408
P22	—	—	—	7000	49.0%	4165.00	—	—	—	—

Microorganisms

Staphylococcus aureus was cultured from all cold skin abscesses. Thus, *Staphylococcus aureus* was the most frequently identified organism. Other bacterial agents were encapsulated organisms such as *Haemophilus influenzae* and *Streptococcus pneumoniae*. Acute pneumonias were mainly caused by *Staphylococcus aureus*, *Streptococcus pneumoniae* or *Haemophilus influenzae*; superinfections of pneumatoceles were associated with *Pseudomonas aeruginosa* and *Aspergillus fumigatus*. Acute diarrhea was mostly caused by *Giardia lamblia*, in addition some episodes of Shigellosis and Salmonellosis were documented. One patient had hepatic hydatid cyst due to *Echinococcus granulosus* (P7) and one patient had a liver abscess due to *Actinomyces israeli* (P16). Two patients had BCG adenitis and skin abscesses (*Bacillus koch*+) following Bacillus Calmette-Guerin (BCG) immunization (P8 and P17). Mucocutaneous candidiasis, as the most common opportunistic infection, was documented in nine patients. Moreover onychomycosis was seen in four cases. Chronic, disfiguring *Molluscum contagiosum* infection was seen in five patients and herpetic keratitis due to severe *Herpes simplex* infection occurred in four patients.

Other Clinical Features

Eczeema/dermatitis was a finding in all patients and neonatal rash has been documented in 18 patients. Thirteen patients (60%) had the characteristic coarse facies, which was much lower than in previous studies [1,8,16,17]. It consists of a prominent forehead, a wide alar base of the nose regardless of race, and a wide outer canthal distance [4]. Pneumatocoles were identified in ten cases. Non-specific findings as hepatomegaly (six cases) and splenomegaly (four cases) were seen. In half of the patients (eleven cases), lymphadenopathy has been recorded in the course of the disease. Other manifestations were ulcerative colitis (P4), alopecia areata (P8), and celiac disease (P14).

While no consistent abnormality in the number or distribution of the lymphocyte subpopulations was observed, four patients had low hemoglobin levels. This anemia may have been caused by chronic lower respiratory tract infections, which were the most common infections but not present in all patients.

Hospitalization related to Infectious Complications

All patients have been hospitalized due to infectious complications. The median duration of the disease

was 14 years (range: 3–28), during which 119 admissions have been recorded (range: 1–14). Hospitalization ranged from 0.07 to 1.33 per patient per year (mean: 0.41 ± 0.29). Although statistical analysis of these data has not shown any correlation between eosinophilia and infectious complications, it was complicated by the fact that patients with higher IgE levels were hospitalized more frequently. A positive association was observed between admission number and serum IgE level ($r = 0.454$, $F = 5.201$, $P\text{-value} = 0.034$).

Mortality

The patients were followed through a period of 8.7 ± 6.9 years. Some of the patients had been followed for up to 21 years; nine patients had been followed for more than 10 years (a total of 192 patient-years). During the follow-up period, five subjects died (1 to 9 years after their diagnosis, P11 in 1998, P13 in 2003, P14 in 2000, P22 in 2004, and P9 in 2005). One of the patients had died because of Hodgkin's lymphoma, a malignancy which has been previously reported in HIES [18,19].

Comparison of Findings between Consanguineous and Non-consanguineous Families

In this report, we describe 13 patients from consanguineous marriages and nine patients from non-consanguineous parents (Table III). The comparison of manifestations between two groups of HIES patients with a history of consanguinity and HIES patients from non-consanguineous families, revealed severe chronic refractory *Molluscum contagiosum* infections in five cases from consanguineous matings only. In addition, four patients from this group also suffered from recurrent aphthoid *Herpes simplex* infections (Table III). Although patients from non-consanguineous families were more prone to abscesses formation and pneumatocoles, patients from consanguineous families had a higher frequency of recurrent upper respiratory tract infections, otitis media; mucocutaneous candidiasis, and hepatosplenomegaly (Table III). P3 and P6, whose parents were not consanguine, suffered from a hip osteoporosis and scoliosis. A bone scan in P3 showed high uptake of radioisotope agent suggesting osteomyelitis and arthritis. P4 and P10, whose parents were consanguine, were both osteopenic. X-ray studies in P10 identified flat vertebrae. No patient presented CNS manifestation unless an infectious complication affected the brain in P14 and brain abscess in P13. Both of these patients were from consanguineous families. Eosinophilia was much higher in patients from consanguineous families, but this is

Table III. Clinical and laboratory findings of HIES patients with a history of consanguinity in comparison with patients from non-consanguineous families.

	HIES from non-consanguineous families (n = 9)	HIES from consanguineous families (n = 13)
Chronic eczema	9 cases (100%)	13 cases (100%)
Neonatal rash	9 cases (100%)	9 cases (69.2%)
Skin abscesses	7 cases (77.8%)	8 cases (61.5%)
Deep abscesses	7 cases (77.8%)	4 cases (30.8%)
Recurrent upper respiratory tract infections	4 cases (44.4%)	11 cases (84.6%)
Otitis media	2 cases (22.2%)	9 cases (69.2%)
Sinusitis	3 cases (33.3%)	5 cases (38.5%)
Recurrent pneumonia	7 cases (77.8%)	10 cases (76.9%)
Pneumatocoles	6 cases (66.7%)	4 cases (30.8%)
Bronchiectasis	2 cases (22.2%)	3 cases (23.1%)
Diarrhea	4 cases (44.4%)	8 cases (61.5%)
Mucocutaneous candidiasis	2 cases (22.2%)	7 cases (53.8%)
Molluscum contagiosum	0	5 cases (38.5%)
Herpes virus complications	0	4 cases (30.8%)
Characteristic coarse face	5 cases (55.6%)	8 cases (61.5%)
Organomegaly	1 case (11.1%)	5 cases (38.5%)
Serum IgE (IU/ml)	>2000–80000	>2000–10000
Absolute eosinophil count (cells/mm ³)	110–6786	590–15834

not significant (3.872.3 vs. 1.459.4, P-value = 0.13). Moreover IgE serum levels were higher in these patients (P-value = 0.38).

Discussion

Hyper-IgE syndrome (HIES) is a rare primary immunodeficiency with unknown etiology [1,4,9]. Although the syndrome was first identified in Caucasians, HIES is also seen in Asian and African ethnicities [20–22]. The present study in Iranian patients with HIES shows an equal distribution between the sexes, while a male to female ratio was 1:2 and 2:1 in previous surveys [2,4].

In our cohort of 22 patients with HIES, in 13 cases the parents of the proband were consanguine (62%), thus an autosomal recessive mode of inheritance can be assumed. This is not surprising, as in Iran and in other countries with the same cultural background consanguineous matings are common.

The serum IgE was grossly elevated in all of our patients. Patients with higher serum IgE levels were admitted more frequently due to severe infections, which is in contrast to the published observation that the level of serum IgE is not related to severity of the disease [1,9,23]. In addition, other major isotypes of immunoglobulin were often elevated, consistent with a general stimulation of humoral immunity [2,11]. Lymphocytes were deficient in CD8+ T cells in the study by Geha, et al [24], but this was not true of our patients. However, one of our patients (P21) was deficient in CD4+ T cells and four patients had a reversed CD4/CD8 ratio.

Complications by *Molluscum contagiosum* and *Herpes viruses* have only been seen in our patients from consanguineous families. This is compatible with previous reports [1,11] and supports the notion that the cellular immunity is critically defective in patients with the AR form of HIES [11].

Pneumatocoele formation following pneumonia has been reported characteristic of autosomal dominant HIES and sporadic HIES and is not seen in patients with the autosomal recessive form of the disease [4,11]. This is in contrast to our observation where pneumatocoles occurred in approximately one third of our patients from consanguineous families.

Ulcerative colitis, alopecia areata, and celiac disease, all indicative of autoimmunity, were seen in three of our patients from consanguineous families. Thus, autosomal recessive HIES differs from autosomal dominant HIES in several key findings and therefore represents a distinct entity as has been suggested before [11].

HIES usually presents early in life. Sixty-eight per cent of our patients presented at least one clinical finding during the first month of life, though none of them was diagnosed before the end of the first year of life. The diagnostic delay (70 months) was higher than previous studies [25]. Diagnosis is complicated by the lack of a reliable diagnostic tool for HIES but relying of a mosaic of characteristic clinical findings [10]. The diagnosis should be considered in case of staphylococcal pneumonias or recurrent abscesses, complicating chronic eczema [9]. An early recognition improves prognosis [23]. A neonatal rash can raise the suspicion if other members of the family are affected.

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