MINERVA MED 2000;91:113-6

Moderate-dose intravenous immunoglobulin treatment of Job's syndrome

Case report

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Job's syndrome (or hyperimmunoglobulinemia E syndrome) is a rare genetic disease characterized by skin eczema, pyogenic "cold" abscesses, sinopulmonary recidivous infections and high IgE plasma concentrations. Job's syndrome treatment is not satisfactory and cases studied are still limited. To describe the effects of IVIG therapy in a 37-year-old woman with hyper IgE syndrome and pneumonia. We measured IgE serum by immuno-fluorometric test and neutrophil chemotaxis by migration in a Boyden chamber before and after IVIG therapy. A moderate dose of IVIG resolved the clinical-radiological signs of the *S. aureus* bronchopneumonia and improved cytologic and biohumoral parameters. Intravenous immunoglobulins represent a useful treatment for acute pneumonia in Job's syndrome.

Key words: **Job's syndrome - IgE - Immunoglobulins, intravenous.**

Job's syndrome is a quite rare genetic disease with autosomic dominant transmission and variable penetrance affecting more frequently the female sex and particularly, patients with recessive somatic types (fair hair and fair complexion).[1]

Job's syndrome is usually diagnosed in early infancy and is characterized by severe eczema, recurrent *Staphylococcal* infections and "cold" subcutaneous abscesses (i.e. with no redness) [2] which sometimes break out into a fulminat necrotizing pattern.[3]

S. aureus with other pyogenes is also responsible for infections of the sinopulmonary tract, while the mucous tissue can be affected by candidiasis.

Osteoporosis and brittle bones were described too.[4]

The disease is characterized, from the immunologic point of view, by immunoglobulin E increase (hence its name hyper-IgE) and, in acute phases, by a granulocytes chemiotaxis deficiency.

Job's syndrome treatment is not satisfactory and cases studied are still limited. We are going to describe one case we studied and the results obtained with medical therapy.

Case report

A 37-year-old young woman, with fair hair, fair complexion and coarse facial features, came to observation. She had been admitted to hospital several times for recurrent bronchopneumonia, with confirmed eosinophilia and IgE increase.

Received November 29, 1999.
Accepted for publication March 31, 2000.

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TABLE I.—*Effects of Ig vein treatment on some laboratory tests.*

Parameters	Day 0	Day 28	Day 56
White blood cells (WBC/mm³)	9.600	8.400	8.100
Eosinophils (%)	20.6	18.1	9.4
Lymphocytes (%)	29.9	34.8	36.8
CD4/CD8 (N=1.5-1.2)	2.6	1.9	1.8
Serum IgE (kU/L)	43.986	26.700	12.700
ERS (mm/1st h)	75	18	9
Neutrophil function (*ZAS)	Reduced	Normal	Normal
(**NBT)	Normal	Normal	Normal

*) ZAS=chemotactic stimulation with activated serum by Zymosan A, **) NBT=nitro blu tetrazolium test.

Since she was ten years old, she suffered from eczema and diffuse skin abscesses causing numerous scars on her back, groin and lower limbs.

Her admission to our Department was determined by a further febrile episode (39.2°C) with cough.

The patient presented quite good general condition and physical examination revealed pneumonic rales with middle-small crackles, particularly in the right base.

Hematochemical parameters showed: eosinophilia (WBC=9600/mm³, eosinophils=20.6%), raised erythrosedimentation rate (ERS) (75 mm/1st h), increase of Ig E (43.986 kU, normal levels<200 kU) and of the CD4/CD8 ratio among the lymphocyte subpopulations (2.6, normal levels: 1.2-2.4), mild reduction of C3 fraction of complement (54 mg/dl levels: 70-160 mg/dl). Immunoglobulins A, G and M, histological features of bone marrow needle aspiration and some common neoplasia markers (embryogenic carcinoma antigen, alfa fetoprotein, Ca 19-9, CA 15-3, CA 125, tissue polypeptidic antigen) were within normal levels (Table I).

Rheumatoid factor tests, antinuclear antibodies, anti-echinococcus antibodies, anti HIV and pathogenetic mycets were negative, as well as Mantoux test (PPD 5U), common allergens sensitivity test (multitest) and faecal eggs and parasite search.

A chest X ray showed parenchymal thickening at the right posteromedial pulmonary base (Fig. 1) confirmed by CT scan and bronchoscopy showed severe subacute purulent tracheobronchitis.

The culture demonstrated *St. aureus* growing colonies (methicillin-resistant). Further instrumental exams (X-ray and computerized tomography) showed right maxillary sinus opacification and no other signs of skeleton involvement except for some mild arthrosis were found.

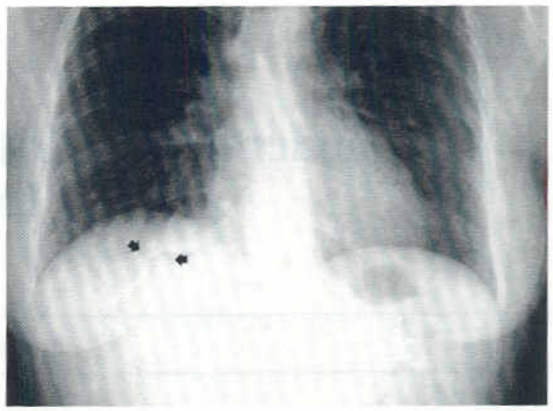

Fig. 1.—Chest X-ray. Parenchymal thickening in the right postero-medial pulmonary basis.

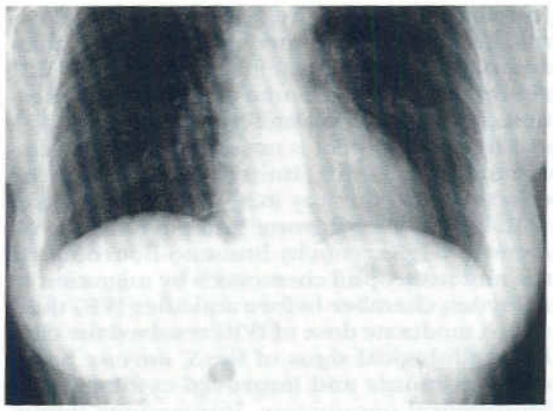

Fig. 2.—Chest X-ray after a week of treatment. Recovery.

Functional leukocyte tests were carried out, such as migration in a Boyden chamber (reduced) and Nitroblue terazolum test (which was normal), (Table I).

Meanwhile antibiotic therapy with Vancomycin 1 g × 2 for 10 days was started without remission of the radiological pattern and with slight clinical improvement. Job's syndrome was diagnosed and the patient was treated with intravenous human immunoglobulin (Ig Vein 5 g/day for 5 days).

A chest X-ray one week later (Fig. 2) showed resolution of the lung infiltrate and improvement of the clinical symptoms. The control of biochemical parameters after 28 days of treatment indicated mild decrease of eosinophils (WBC=8400, E=18.1%) and more remarkably decreased ERS (18 mm/1st h) and IgE (26.700 kU). A normalization of leukocytes chemotaxis, ERS (18 mm/1st h) and IgE decrease (12.700 kU) were even more evident after 56 days (Table I).

Thus the patient was preventively treated with monthly moderate IVIG (5g/day for 5 days) during the Winter time (December, January, February). Nev-

ertheless, the patient had another pulmonary Staphylococcal infection, still resistant to ordinary therapy, that healed with the support of moderate doses of IVIG.

Discussion and conclusions

The molecular defect responsible for Job's syndrome has not yet been identified. Some a. hypothesize that IgE increase is connected with T lymphocytes suppressor relative deficiency. That is pointed out by the increased CD4+/CD8+ ratio in the lymphocyte population which are unable to inhibit IgE production.[5,6]

Other researchers reported that plasma cells secreting IgE in the disease progression and this appears unrelated with interactions with other cells or from modulation of gamma interferon and interleukins.[7]

Even if adequate in number, neutrophils are likely to show defective chemotaxis in connection with high IgE concentration.[8,9]

Besides typical clinical manifestation, the case described appears at an older than usual age. Although the disease may be more common in childhood, nevertheless it has been described patients of quite different age (range 3-66 years m Hill HR series).[10] From a general point of view, the presence of human immunodeficiency virus (HIV) infection is to be excluded.

In the course of Acquired Immunodeficiency Syndrome (AIDS), patients had features similar to those present in hyper-IgE syndrome: atopy, subcutaneos abscesses, allergies and plasma IgE increase which was twice to four times the highest normal levels.[11] In those cases pathogenesis was probably different since the CD4+ and CD8+ lymphocytes ratio, instead of increasing, appeared reduced.[12] In our case CD4/CD8 ratio was high, and the HIV antibodies search proved negative, leukocytes chemotaxis reduced whilst IgE plasma levels were much greater than those described in AIDS cases associated with hyper-IgE, as well as in other hyper IgE syndrome cases in the literature.[10]

It has to be emphazised that some cases of hyper IgE syndrome were associated with lymphoma development:[13] pathogenetic relations are still to be determined, anyway.

With regards to therapy, gamma interferon,[10] plasmapheresis,[14] cyclosporin [15] or intravenous immunoglobulin [16] treatments have been suggested. After 5 days of this high dose treatment, according to a protocol similar to our patient's, results looked the most promising: described cases [16] responded with a dramatic decrease of Ig E levels and with remarkable clinical improvement.

IgE levels decreased markedly in our patient but to a lower degree, whereas leukocyte function as well as the global clinical results improved (recovery of the pulmonary Staphylococcal infection). Differences may be more likely due to the moderate doses we used for prudential reasons.

There were no effects of prophylactic therapy with IVIG, but that was beneficial during the acute illness phases; for these encouraging results we suggest the consideration of moderate IVIG dosage for treatment of infection in patients with hyper IgE syndrome.

Riassunto

Il trattamento della sindrome di Job con moderate dosi di immunoglobuline. Descrizione di un caso.

La sindrome di Job (o sindrome da iper IgE) è una rara malattia genetica caratterizzata da eczema cutaneo, ascessi «freddi» da piogeni, broncopolmoniti ed infezioni recidivanti dei seni mascellari oltre ad un aumento delle IgE plasmatiche. La terapia della s. di Job non è attualmente soddisfacente anche per la casistica limitata. L'obiettivo di questo lavoro è stato descrivere gli effetti della terapia con IgG vena in una donna di 37 anni affetta da polmoniti recidivanti ed aumento delle IgE. Abbiamo misurato le IgE seriche con test immuno-fluorimetrico e la chemiotassi dei neutrofili mediante migrazione in una camera di Boyden prima e dopo terapia con IgG vena. Moderate dosi di IgG vena hanno determinato la guarigione della broncopolmonite da *S. aureo* ed hanno migliorato sia i parametri bioumorali che citologici risultati alterati in questa sindrome. Le immunoglobuline endovena rappresentano un'utile terapia della broncopolmonite nella sindrome di Job.

Parole chiave: Sindrome da iper IgE, terapia.

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