CLINICAL CASE

Hyperimmunoglobulin E syndrome: report of two cases

Síndrome de hiperinmunoglobulinemia E. Reporte de dos casos

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Abstract

Background. Hyperimmunoglobulin E (hyper IgE) syndrome is a rare systemic immunodeficiency characterized by eczematous dermatitis, recurrent cold abscesses, lung infections with pneumatoceles, coarse facial appearance, high IgE levels and eosinophilia.

Case reports: *Case 1*: We report the case of an 11-year-old female with a history of recurrent lung infections, recurrent gastroenteritis, eczematous dermatitis affecting the skinfolds and cold abscesses. Laboratory studies showed elevated eosinophils (16,070) and IgE (4864 IU). The patient received treatment with gammaglobulin, showing adequate clinic response to treatment. *Case 2*: We present the case of a 12-year-old female with a history of recurrent otitis and suppurative conjunctivitis, showing widespread and chronic infected eczema. Laboratory studies showed elevated IgE (3000 IU). The patient was treated with dapsone, trimethoprim/sulfamethoxazole and methotrexate.

Conclusions. We report on two patients with eczematous skin, recurrent infections and increased IgE levels, which are compatible with hyper IgE autosomal recessive syndrome.

Key words: hyperimmunoglobulin E syndrome, Job's syndrome, eczema, lung infection, cold abscesses, congenital immunodeficiency.

Resumen

Introducción. El síndrome de hiperinmunoglobulinemia E es una inmunodeficiencia sistémica poco frecuente, caracterizada por dermatitis eccematosa, abscesos fríos recurrentes, infecciones pulmonares con formación de neumatoceles, facies tosca, niveles elevados de inmunoglobulina E (IgE) en suero y eosinofilia.

Casos clínicos. Caso 1. Femenino de 11 años de edad con antecedentes de neumonía recurrente, gastroenteritis de repetición, dermatitis eccematosa de predominio en pliegues, y abscesos fríos; en estudios de laboratorio destacó el hallazgo de 16 070 eosinófilos e IgE de 4 864 UI. Manejada con gammaglobulina se observó buena respuesta clínica. Caso 2. Femenino de 12 años de edad con historia de otitis recurrente y conjuntivitis supurativa, presentaba eccema crónico generalizado e impetiginizado. En estudios de laboratorio se reportó IgE de 3 000 UI; fue manejada con dapsona, trimetropim/sulfametoxazol y metotrexate.

Conclusión. Los 2 casos aquí informados presentaron piel eccematosa, infecciones recurrentes e incremento de los niveles de IgE, compatibles con síndrome de hiperinmunoglobulinemia E en la forma autosómica recesiva.

Palabras clave: Síndrome de hiperinmunoglobulinemia E, síndrome de Job, eccema, infección pulmonar, abscesos fríos, inmunodeficiencia congénita.

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Hyperimmunoglobulinemia E syndrome (hyper IgE syndrome) was first described in 1966 by Davis et al.[1] when reporting on two females with red hair, severe chronic dermatitis, cold abscesses and recurrent pneumonia. They referred to this disease as Job's syndrome in reference to the biblical character Job, whose faithfulness was tested to withstand ulcers and draining fistulas that he suffered for life. Later, in 1972, Buckley et al.[2] described this syndrome in two children with severe dermatitis, recurrent abscesses in the skin, lungs and joints, growth retardation, coarse facies and exaggerated immediate hypersensitivity associated with elevated levels of immunoglobulin E (IgE) in serum and eosinophilia. This is also known as Buckley's syndrome. However, we are trying to omit the eponyms and recommend referring to this condition as hyper IgE syndrome. This condition is due to a genetic defect that causes the production of elevated serum IgE antibodies. Eczema and recurrent infections are characteristic. It is an extremely rare disease. To date there have been only ~250 cases reported in the literature.[3] In most cases it is inherited as an autosomal dominant gene and predominately shows dental manifestations and bone disorders.[4] The autosomal recessive trait is associated with serious viral or fungal infections. The use of high-dose IV gammaglobulin has been effective in the treatment of this disease. In this article we report on two cases of hyper IgE syndrome as an autosomal recessive trait.[5,6]

Clinical cases

Case 1

We report the case of an 11-year-old female patient who was a native and resident of Zimapam, Hidalgo and was hospitalized in a tertiary level institution with a diagnosis of pneumonia (Figure 1). We requested a consultation with the Dermatology Service for the presentation of disseminated bilateral, symmetrical dermatitis that affected the corners of the mouth, neck, axillary folds, and antecubital, inguinal and vulva regions; dermatitis consisting of large ill-defined plaques comprised of erythema, meliceric and hematic scabs, exulceration and eczematous-looking skin. In other areas there was predominately liquefaction, hematic scabs and residual hyperpigmentation. At an axillary and inguinal level there was an increase in volume and of fistulas with purulent material discharge with no increase in temperature or local erythema (cold abscesses) (Figure 2). The patient presented with malnutrition (weight 23 kg and height 125 cm). With respect to her facial features, her nasal bridge was broad with a round tip (Figure 3).

During an indirect questioning, there was a reference to a rash at birth, which improved with an unspecified topical treatment and, from 5 years of age, she presented lesions similar to those already described, going through periods of partial remissions and exacerbations.

Laboratory results showed eosinophilia of 82% (0-7% normal) with an absolute count of 16,070 (0-0.8/μL) eosinophils and an IgE of 4864 IU/mL (0-100). Interleukin (IL)-12 and IL-2 were decreased and interferon-γ and IL-4 were reported

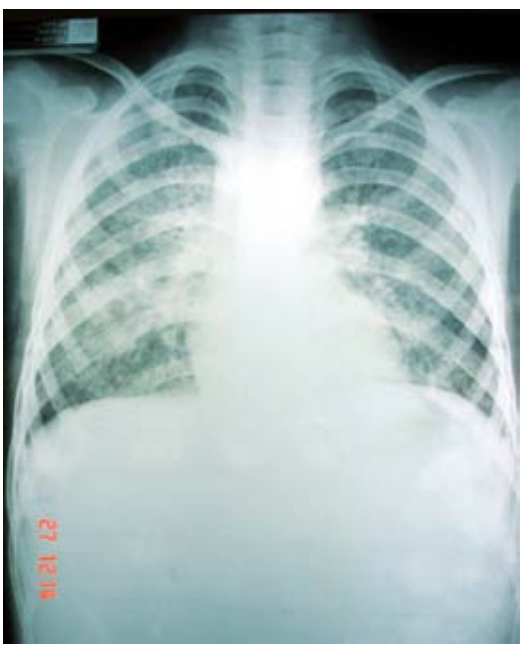

Figure 1. Case 1. Chest x-ray where there is pulmonary parenchyma with reticulo-micronodular and macronodular image.

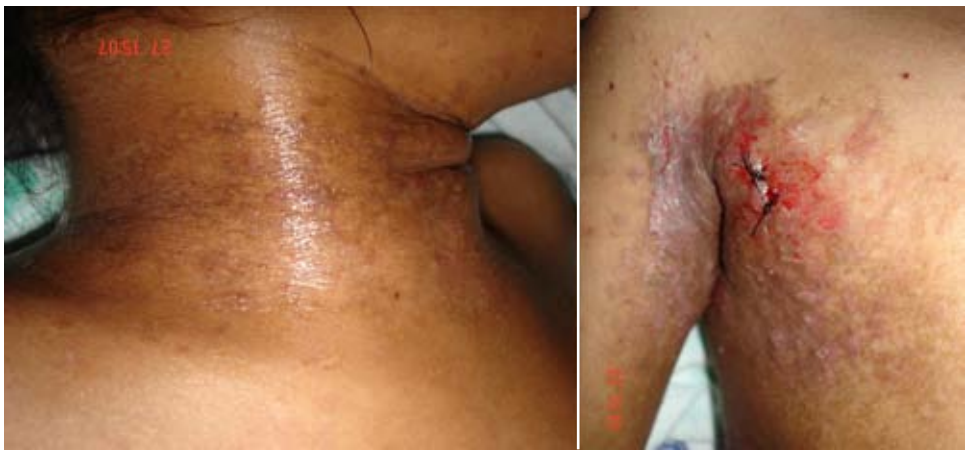

Figure 2. Case 1. Eczematous dermatitis predominantly in flexural areas.

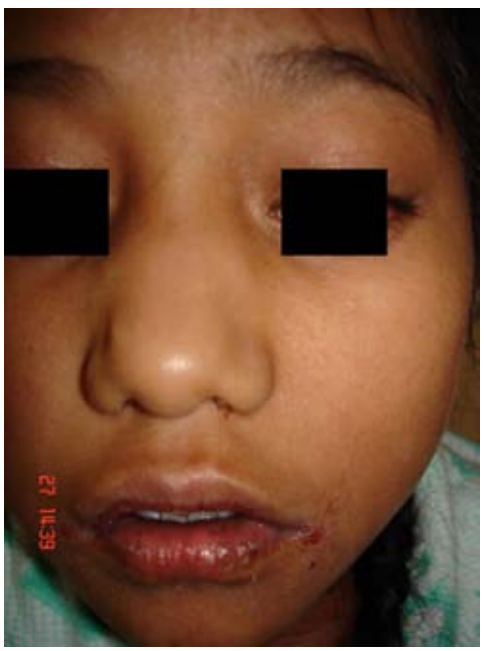

Figure 3. Case 1. Patient with broad nasal bridge and tip, lower lip thickness and eczema at the level of lip commissures.

slightly increased, with normal values of NK cells. Coproparasitoscopic exam revealed cysts of *Giardia lamblia*, which were treated with metronidazole.

With the presented data we originally considered a diagnosis of atopic eczema; however, our attention was drawn to the history of two hospitalizations at 4 and 7 years of age due to pneumonia, which were treated with clarithromycin, ketoconazole and cefatoxime. In addition, there was a history of recurrent gastroenteritis since the age of 5 years, with foul-smelling, mucus-containing stools. At the age of 10 years, the patient developed a cold abscess in her skin and in 2005 she had cultures taken from an inguinal lymph node. This was reported as adiaspiromycosis-positive PAS due to *Chysosporium parvum*. In 2006, a pulmonary biopsy was performed due to an unusual radiopaque image on chest x-ray, reporting granulomatous lesion. PPD skin test was negative.

Directed questioning ruled out parental consanguinity. The patient was the product of the eighth pregnancy, with two deceased brothers, one at the age of 1 year due to an unspecified dermatological condition and the other due to a septic infection. The rest of the siblings were considered to be healthy.

From the gathered data, we decided to perform a skin biopsy, which suggested the diagnosis of eczema secondary to hyper IgE syndrome vs. chronic granulomatous disease.

Skin histopathology showed spongiosis, focal vacuolization of the basal layer, exocytosis of eosinophils, deep and superficial perivascular interstitial inflammatory infiltrate consisting of eosinophils, lymphocytes and histiocytes (Figure 4).

Diagnosis of hyper IgE syndrome was corroborated. The patient was treated during her hospitalization with ceftriaxone and amikacin for the pneumonia and topically for the eczema with mupirocin mixed with aceponate of methylprednisolone twice daily and with warm soaks. She demonstrated a good

response to treatment and was discharged from the hospital with prophylaxis based on trimethoprim/sulfamethoxazole and itraconazole. Gammaglobulin doses of 400 mg/kg were initiated.

Three months after her discharge, the patient was hospitalized with infected bronchiectasis. Sputum culture reported *Entamoeba coli* and *Branhamella catarrhalis*. Eosinophilia was 90% with 17,480 total eosinophils. She was treated with ceftriaxone, amikacin, and gammaglobulin (500 mg/kg). Upon her discharge, it was decided to increase the gammaglobulin by 1 g/kg, with a good clinical response.

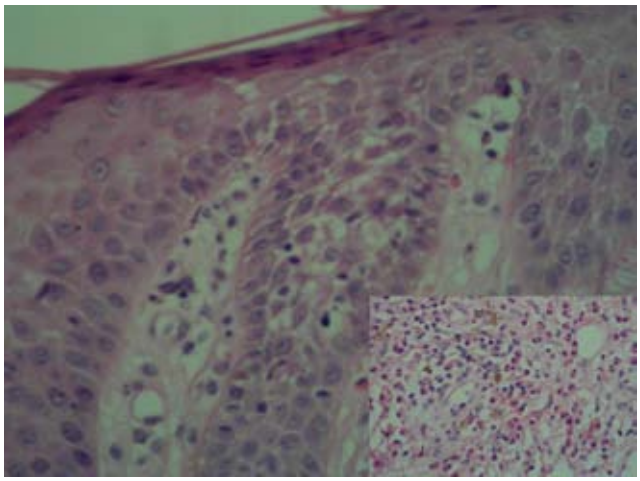

Figure 4. Case 1. Histological study of skin showing epidermis with focal spongiosis and vacuolization of the basal layer (H-E ´40). Lower panel shows inflammatory, diffuse perivascular infiltrate composed of eosinophils, loss of pigment and melanophages (H-E ´60).

Case 2

We report the case of a 12-year-old female patient who was a native and resident of Oaxaca, Mexico. She was admitted to a pediatric hospital with the diagnoses of generalized impetigo, conjunctivitis, and suppurative otitis media.

There was a consultation with the Dermatology Service for the presentation of widespread, bilateral and symmetrical dermatitis affecting all parts of the body. The scalp contained patches of pseudo-alopecia, scales, and meliceric and hematic scabs. Papules, pustules, and eczematous impetiginized patches were observed on the rest of the body, as well as maceration of the skinfolds (Figure 5). Physical examination revealed submandibular, axillary and inguinal lymphadenopathy with 5 months of evolution. Dermatitis began in skinfolds with gradual spread. It was treated with copper sulfate (1:1000), diclox-

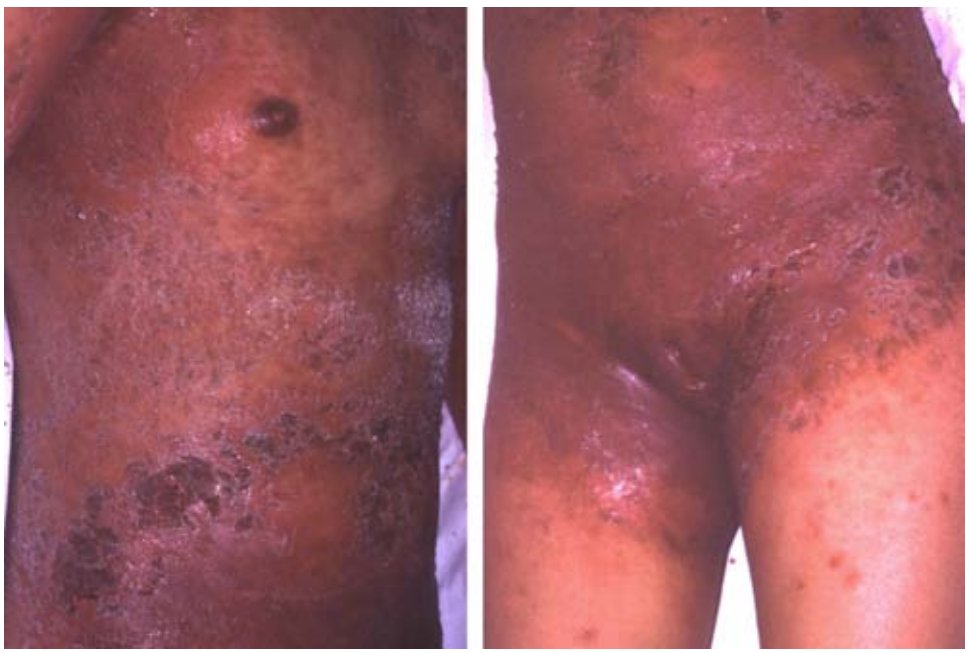

Figure 5. Case 2. Generalized dermatosis consisting of papules, pustules, and eczematous impetiginized patches.

acillin, chloramphenicol ophthalmic and loratadine/betamethasone (5 mg/0.25 mg) every 8 h. From the laboratory results the following were highlighted: leukocytosis, eosinophilia and bandemia with discharge culture resulting positive for *E. coli*. She was discharged from the hospital due to improvement. Diagnostic impression was impetiginized atopic dermatitis.

Two months later the patient was back in our care with a fever of unknown origin, conjunctival hyperemia, greenish eye discharge, otitis externa and generalized eczema, so again she was hospitalized. She was treated with copper sulfate, vioform and dicloxacillin for the suspected diagnosis of atopic dermatitis impetiginized (positive culture for *Staphylococcus aureus* and *E. coli*). She was given hydroxyzine (1 mg/kg/day), prednisone (0.7 mg/kg/day) and isoniazid (300 mg/day) as prophylaxis for tuberculosis due to a history of Coombs+. We performed the biopsy for histopathological study, which showed spongiosis of the epidermis and inflammatory infiltrate of lymphocytes and eosinophils.

Given the history of recurrent otitis externa (Figure 6), which is why the patient came regularly to the Otorhinolaryngology Service, and also due to the episodes of generalized impetiginized eczema and conjunctivitis, it was established that she had a probable diagnosis of hyper IgE syndrome. We identified serum IgE levels with a value of 3000 IU (0-100 IU/mL reference value), which was used to confirm the diagnosis. The patient was discharged with dapsone (100 mg/day), trimethoprim/sulfamethoxazole (160/800 mg/day) and methotrexate. The patient did not return for follow-up. There were no signs of parental consanguinity or any other significant family history.

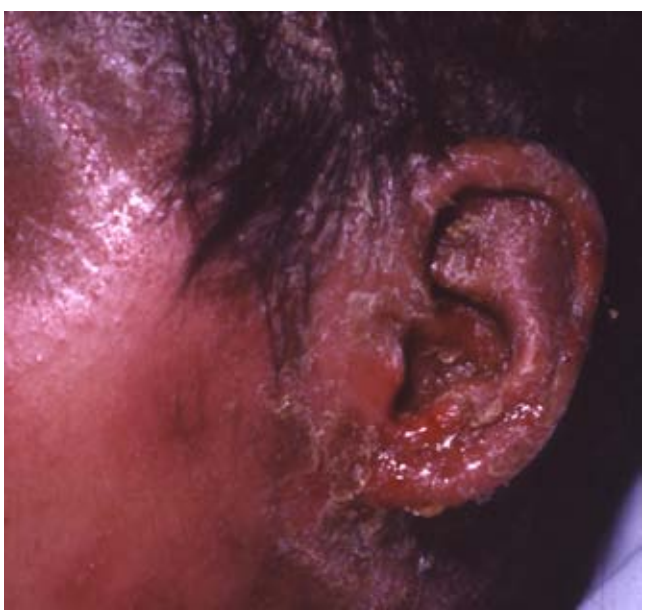

Figure 6. Case 2. Abundant purulent otorrhea.

Discussion

Hyper IgE syndrome is a rare systemic immunodeficiency characterized by the classic triad of high levels of IgE, eczema and recurrent infections. Its incidence is 1/500,000 live births and without gender predominance. Currently, there are ~250 cases reported in the literature.[3] The most common form of transmission is autosomal dominant with variable penetrance. From cytogenetic studies it has been suggested that the alteration is at the level of the long extension of chromosome 4, with a predominance of dental manifestations and bone changes.[4] As for the autosomal recessive transmission, the Tyk2 gene mutation has been determined. It is characterized by the presentation of serious fungal or viral infections and central nervous system manifestations, possibly resulting in ischemic stroke along with subarachnoid hemorrhage and hemiplegy.[5,6] Recent studies have pointed out as crucial in the etiology of this syndrome dominant or sporadic mutations in the STAT3 gene. This gene is directly involved in the response of monocytes to IL-6. Consequently, a decrease occurs with the monocyte chemoattractant protein 1. It also plays a role in the development and differentiation of B cells and Th 17 cells and in the signaling of other cytokines such as IL-10 and IL-17.[7-11]

In these patients a decreased neutrophil chemotaxis exists. It is believed that the pathogenesis is involved in the decrease of C3b receptors on neutro-

phils as well as the decreased molecule of L-selectin adhesion on granulocytes and lymphocytes.[12]

Elevated serum IgE is associated specifically with the formation of antibodies against *S. aureus*. It is characteristic to find levels of IgE >20 times its normal value (>2000 IU/mL), with an elevated eosinophil blood count. Eosinophilia is associated with an increase in the production of granulocyte macrophage colony-stimulating factor (GM-CSF) and decrease of TGF-β. IL-4 is usually normal. There is also decreased production of interferon-γ and tumor necrosis factor, with a poor response to IL-12 stimulation, decrease in the population of lymphocyte B memory cells and delayed hypersensitivity response. There is an increase in the production of reactive oxygen intermediates by the neutrophils, which explains the tissue damage.[13,14]

In previous studies, changes associated with the syndrome have been described, with the classic triad of skin abscesses and recurrent pneumonia, in addition to elevated levels of IgE. Severe eczema is a universal fact.[15,16] Likewise, characteristic coarse facies is described without the appearance of being completely dysmorphic. The most-relevant craniofacial features are the prominent eyebrows, with the appearance of sunken eyes, broad nasal bridge and tip, thick lower lip, facial asymmetry, prominent forehead, hypertelorism, prognathism and rough facial skin with large pores.[17] Only the patient described in the first case (Case 1) had these characteristics.

In an attempt to establish early data of the disease, it has been observed that 74% of patients have pruritis prior to the age of 2 years, 72% have a history of flexural eczema, and 81% of newborns have a history of a rash during the first month of life. Although we have not yet established the early data for diagnosis because initially the principal characteristics such as eczematous dermatitis are not presented, some authors propose to consider hyper IgE syndrome within the differential diagnosis of macules, papules, vesicles, pustules in newborns.[18-20] The patient described in Case 1 has a history of a rash at birth and at the time of the consultation there was eczema and liquefaction, frequent lesions in patients with atopic dermatitis. The patient described in Case 2, in addition to eczema with secondary impetiginization, is remarkable with a history of recurrent ear infections and conjunctivitis. Patients with autosomal recessive hyper IgE syndrome present viral infections more frequently from molluscum contagiosum and herpes simplex. In addition, these patients have a high frequency of central nervous system disorders.[5] These data were not found in the cases reported here.

Among the dental abnormalities reported are the primary retention of the teeth or the lack of eruption of the permanent teeth, the presence of primary teeth and permanent teeth at the same time and the elevation of the palate. The patient described in Case 1 had a history of delayed dentition; nevertheless, during physical examination no dental abnormalities were found.[21,22]

With regard to treatment, there is yet to be one specific cure so therapeutic treatment decisions are based on clinical manifestations. The most effective therapy is the use of systemic prophylactic antibiotics with coverage directed against *S. aureus*. There are case reports of clinical and immunological improvement of eczematous dermatitis, decreased frequency of cold abscesses, IgE and eosinophilia with continued use of trimethoprim/sulfamethoxazole (40 mg/kg/day/8 mg/kg/day). Nevertheless, the evaluated *in vitro* effects of this antibiotic at the level of neutrophil chemotaxis and production of hydrogen were not reproducible. At this time the mechanism of action remains unknown.[23,24] It has been reported that the use of IV immunoglobulin in some cases has had unsatisfactory results;[25] however, another study by Kimata[26] mentions an appropriate response to the treatment with high-dose IV gammaglobulin (400 mg/kg/day) for 5 days. This author observed a reduction in the severity of the eczema in addition to a decrease in IgE production *in vivo* and *in vitro*.[27-29] Another drug used is interferon-γ, which increases the basal chemotactic index.[27] Reports exist of successful cases from secondary therapeutic use of isotretinoin, whereas the possible mechanism of action is still unknown.[28]

With regard to the predisposition to malignancy, to date an increase has not been proven. There have only been reports that mention an association with hematological malignancies.[30-34]

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