

Review Article

Hyperimmunoglobulin-E syndrome with recurrent infection: A review of current opinion and treatment

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Hyperimmunoglobulin E (hyper-IgE) syndrome with recurrent infection is a rare idiopathic primary immunodeficiency. It consists of a severe dermatitis with recurrent abscess formation, respiratory tract infections and very high titres of serum immunoglobulin E (IgE). Hyper-IgE syndrome is also associated with skeletal abnormalities. Variability of presentation makes it easy to confuse the diagnosis with that of severe atopy or other rare immunodeficiencies. The aim of this article is to review the literature in order to consider the clinical findings, etiology and treatment of this syndrome.

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Hyperimmunoglobulin E (hyper-IgE) syndrome has not been recently reviewed in English (1). A literature search was performed using Medline Express with the terms Hyperimmunoglobulin*E, Hyper IgE, Job syndrome and Buckley syndrome between 1966 and 2000 inclusive, with follow-up of references from those papers. The evidence-based quality of published studies is limited by the scarcity of affected individuals. This has promoted case reports and a few case series. There is therefore a reliance upon good, old-fashioned anecdote and experience.

Job's syndrome

Part of the confusion surrounding hyper-IgE stems from the several names for the condition. It was first described by Buckley, Wray and Belmaker in 1972 (2). However, it is sometimes referred to as Job's syndrome after an earlier report of two girls who had skin abscesses and severe infections (3). The skin of these two girls was so badly affected that the syndrome was named after the Prophet Job's diabolical dermatitis (Job 2 : 7). It was initially disputed that Job's

syndrome was a variant of chronic granulomatous disease (CGD), as both disorders presented with abscesses and had a neutrophil function defect. However, unlike CGD, the nitrazolium blue test was found to be normal in Job's syndrome (4). Following this discovery, elevated levels of IgE and a defect of neutrophil chemotaxis were identified in the two Job's-syndrome girls (5). This shows that Job's syndrome and hyper-IgE syndrome are probably the same condition. To remove any further confusion the least ambiguous, but cumbersome, name is that of the 'hyper-IgE syndrome with recurrent infection'.

Presentation

Where other members of the family are affected, the diagnosis can often be made in infancy with the onset of a distinct neonatal rash. Otherwise, the diagnosis should be considered in children with staphylococcal pneumonias or recurrent abscesses complicating chronic eczema. The syndrome is not that of severe atopic eczema with repeated skin infection (6). There is typically an absence of atopic symptoms, wheeze or family history of atopy.

Table 1. Clinical and laboratory criteria for diagnoses of hyperimmunoglobulin E (IgE) syndrome using the Grimbacher criteria (7)

Study (ref.)	Davis et al. (3)*	Buckley et al. (2)	Buckley & Becker (12)**	Donabedian & Gallin (10)	Leung & Geha (8)	Grimbacher et al. (11)	Borges et al. (9)
Number of patients	2	2	20	13	9	30	9
Laboratory values							
Mean highest serum IgE (IU/ml)	11 955	13 125	20 275	22 067	27 500	20 443	raised 100%
Mean highest eosinophil count (cells/mcl)	437	9%		796		1061	
Skin [n (%)]							
Neonatal rash	2 (100)	2 (100)	9 (45)		9 (100)		9 (100)
Eczema/dermatitis	2 (100)	2 (100)	20 (100)		9 (100)	30 (100)	9 (100)
Skin abscesses	2 (100)	2 (100)	20 (100)	12 (92)	9 (100)	26 (87)	7 (78)
Candidiasis		2 (100)		7 (54)	5 (56)	25 (83)	7 (78)
Infections [n (%)]							
Pneumonia	2 (100)	2 (100)	20 (100)	12 (92)	9 (100)	26 (87)	9 (100)
Parenchymal lung abnormalities	1 (50)	2 (100)	20 (100)	2 (15)	5 (56)	23 (77)	3 (33)
Recurrent serious URTI	1 (50)	2 (100)	most	9 (69)	9 (100)		
Other serious infections				11 (85)			
Lymphoma							
Fatal infection		1 (50)					
Facial and dental [n (%)]							
Characteristic coarse facies	2 (100)	2 (100)	19 (95)	9 (69)	6 (67)	25 (83)†	9 (100)
Retained primary teeth						18 (60)‡	
Increased nasal width							9 (100)
Midline anomaly						3 (10)	
Skeletal [n (%)]							
Scoliosis						19 (63)§	
Pathological fractures					3 (33)	16 (57)	
Joint hyperextensibility	1 (50)					19 (63)	

*Includes data from (5) and (9).

**Includes the two patients originally described (2).

†100% patients by 16-year-old.

‡72% patients by 8-year-old.

§76% of patients by 16-year-old.

There is marked variation in the constellation of symptoms and signs that constitute the diagnosis. A clinical tool for diagnosis does not exist and there is no definitive laboratory investigation. The nearest clinical definition of the syndrome was proposed recently by Grimbacher et al. (7). They created a scoring system to demonstrate the involvement of other family members for inheritance studies. Used in isolation, the Grimbacher score will still misdiagnose hyper-IgE syndrome because it was not designed for this purpose and does not possess any exclusion criteria.

The following clinical features have been described and are summarized in Table 1. The clinical descriptions are based around the original reports and the few published series of the condition (2, 3, 6, 8–12).

Skin involvement

As one would expect from Job's syndrome, the skin disease is severe. It is common for an atypical dermatitis to occur in the first few weeks of life.

Although like eczema, it is disputed that the rash is actually that of atopic dermatitis (6, 8). Skin biopsy reveals an eosinophilic infiltrate similar to that seen in eosinophilic pustular folliculitis (13).

The rash is typically pruritic, often lichenified, and in a distribution atypical for true atopic dermatitis. The pruritus may be secondary to intradermal mast cell histamine release triggered by the elevation of available IgE (14). Similar mechanisms probably exert themselves in senile erythroderma (15).

Skin infections are frequent and start in infancy. They include furuncles, cold abscesses and cellulitis. There are multiple staphylococcal abscesses on the skin (furunculosis) that are most common around the face and are tender and warm to the touch. In addition, 'cold' abscesses are occasionally seen and are pathognomic to hyper-IgE syndrome but not essential to the diagnosis. A cold abscess is a large fluctuant mass that feels like a tumour or cyst. It is neither hot nor tender and is not associated with systemic symptoms, fever or other signs of local or generalized inflammation.

The abscess is filled with pus that always grows *Staphylococcus aureus*. They have been imaged using Gallium isotope scintigraphy (16).

Respiratory tract infection

Pulmonary infections are recurrent and severe. The most common infecting organism is once again *S. aureus*. The pneumonias are frequently complicated and may require surgical intervention. Long-term complications include bronchiectasis, bronchopleural fistulae and pneumatocele secondary to staphylococcal pneumonia. It has been suggested that staphylococcal pneumonias with pneumatocele formation are essential for the diagnosis of hyper-IgE syndrome, but they are not always present in otherwise typical presentations (6). The upper respiratory tract is also chronically infected causing sinusitis, discharging otitis media, otitis externa and mastoiditis.

Mucocutaneous candidiasis and fungal infection

Fungal infections including oral moniliasis are common. The nails are often chronically infected and dystrophic secondary to *Candida albicans*. Deeper *Candida* infections can also occur. *Aspergillus* infection was described in one Job's syndrome patients (17), and cryptococcal infection has also been reported (18, 19).

Other infections

Skin, sinopulmonary and bone infections are the most common. *Staphylococcus* is the most frequently infecting organisms. The threat of methicillin-resistant staphylococcal (MRSA) infection remains a concern (20). There is a wide spectrum of other bacterial infections with mainly encapsulated organisms such as *Haemophilus* and *Streptococcus pneumoniae*. Opportunistic infections are also reported including *Pneumocystis carinii*, normally associated with T-cell deficiencies. The immune response to mycobacteria has also been shown to be atypical, including *Nocardia* infection (21) and disseminated infection following bacille Calmette–Guérin (BCG) immunization (22).

Skeletal and dental abnormalities

Skeletal and facial abnormalities have always been associated with the hyper-IgE syndrome. Borges (1998) has defined the characteristic facies of those affected (9). The typical appearance is universally present after 16 years of age and was

identified in the original Job's syndrome patients from photographs. The appearance is coarse-featured and consists of a prominent forehead (frontal bossing), wide alar base to the nose, regardless of race, and a wide outer canthal distance. This development of a coarse facial appearance has been seen to evolve in a case of late-onset hyper-IgE syndrome (23). As such, it may be secondary to the underlying disease process as opposed to a primary genetic predisposition. Craniosynostosis has also been reported but is unusual (24–26).

It is common for patients to have retained primary teeth that require dental extraction (27). This manifests as two rows of teeth as the primary fail to shed. Other, more unusual, facial anomalies include midline facial defects and a high, arched palate (11).

Long bone fractures occur to minor trauma and may be recurrent (28). Hyper-IgE syndrome has also been associated with one case of osteogenesis imperfecta tarda (29). Osteopaenia was initially described radiologically (30). It has also been demonstrated by absorptiometry (31). Only three of the six patients investigated had pathological fractures. Decreased bone mineral density is not predictive of fracture. Grimbacher et al. found that bone density was decreased in five of nine patients that they tested by densitometry (11). Fractures had occurred in two of those with reduced mineral density and three of those with normal bone density. This osteopaenia may be due to a cytokine-mediated bone resorption process, involving monocytes and prostaglandin E₂ (PGE-2) (31). The cytokine profile in hyper IgE has a similar effect on bone resorption as that of postmenopausal women (32).

Other associations

Hyper-IgE syndrome has been associated with isolated reports of autoimmune disease including systemic lupus erythematosus (33–35), dermatomyositis (36), and membranoproliferative glomerulonephritis (37). Malignant change has also been reported as Hodgkin's disease (38) and lymphoma (39, 40).

Routine laboratory findings

The serum polyclonal IgE is grossly elevated. A lower limit of 2000 IU/ml is used as an arbitrary cut-off for this syndrome. Not all patients with the syndrome will fulfil this criterion, especially in infancy when normal ranges should be considered. The level of serum IgE is not related to

disease severity. Once elevated, serum IgE levels are normally stable. However, a gradually declining level has been reported in six patients over 5 years (11). Anti-*Staphylococcus* and anti-*Candida* IgE titres are raised but the relationship to the disease is not known (41, 42). These titres may be raised before the first significant infection and as such can act as a marker for early diagnosis (43). Unfortunately, raised anti-staphylococcal titres are also seen in atopic patients and are therefore not diagnostic of hyper-IgE syndrome (44). There is also an accompanying eosinophilia that is at least 2 standard deviations above normal, and is normally above 700 cells/mcl (6).

Genetics

Hyper-IgE syndrome is rare and there are no published reports of its incidence. It is found equally in males and females. Although the syndrome was first identified in Caucasians, hyper-IgE syndrome has also been seen in those of Asian and African origin (45, 46). The initial report involved two girls with red hair. Red hair has been reported since then but is an uncommon finding (3, 9).

There is a familial tendency that follows an autosomal dominant pattern with variable penetrance (11, 47). Skeletal and facial abnormalities have always been associated with the syndrome, but it has only been recently that it has been considered a multisystem disorder (11).

Linkage to a region on chromosome 4q has been demonstrated in several affected families (7). This region of 4q has not been sequenced and to date, no candidate gene has been forwarded. A microdeletion involving several genes, which could account for multisystem involvement, has not been reported in this region. On chromosome 16, an up-regulating mutation in the interleukin-4 (IL-4) receptor gene has been demonstrated in atopy and hyper-IgE syndrome (48). Whilst this would provide a mechanism for the immune defect, it has not been found in all patients with hyper-IgE syndrome (49). However, the phenotype for the disorder is variable and it might be that mutation in several different genes can cause the syndrome.

Aetiology

The underlying cause of hyper-IgE syndrome is still unknown. There is a search for the lesion that will unify the immunological with the skeletal aspects of the syndrome. It is likely that the

observed neutrophil chemotactic defect and the raised IgE titre are part of the effect of the syndrome and not the underlying cause.

Originally, hyper-IgE syndrome was considered to be due to a defect in neutrophil function. A reduction in neutrophil chemotaxis was first demonstrated in atopic children with eczema and recurrent skin infections (50). The same mechanism was found to be at work in the hyper-IgE syndrome (5). The defect of neutrophil chemotaxis has been demonstrated by various assays, in response to endotoxin-activated serum, C5a, sodium caseinate and fmet-leu-phe. Other assays of neutrophil function, including oxidative burst assay using the nitroblue tetrazolium (NBT) test are normal (4).

The chemotactic defect is not a constant feature and may vary within a patient over time (10). Therefore it is difficult to establish laboratory end-points for treatment outcomes (51). It appears to be secondary to the production of inhibitory cytokines by lymphocytes (52).

The defect may well lie within the T cell. There are poor antibody responses to immunization, which suggest a fundamental deficiency of the cellular immune response (2, 53). Raised levels of serum IgE are not limited to the hyper-IgE syndrome and are seen in other primary T-cell deficiencies such as the di George and Nezeloff syndromes (12, 54). Kikkawa et al. described a patient with a Nezeloff variant, hyper IgE and thymic aplasia (55).

Gross abnormalities of T-cell numbers and function have not been described in hyper-IgE syndrome. However, further indirect evidence for T-cell involvement is seen in human immunodeficiency virus (HIV) infection, as a hyper-IgE-like syndrome can occur amongst patients infected with this virus (56). Certain T-cell leukaemias can also produce a raised serum IgE (57, 58).

Immunoglobulin E synthesis is a complex process and a defect in regulation could occur anywhere along its path. Simply, IgE regulation involves T-cell stimulation, appropriate cytokine production, several different receptor signalling events and the ability of B cells to class-switch into IgE manufacture (6, 59). The question remains as to the exact nature of the lesion in hyper-IgE syndrome.

T-cell cytokine signalling has been investigated in hyper-IgE syndrome. IgE synthesis is normally enhanced by the T-helper 2 (Th2) cytokines IL-4 and IL-13 and repressed by T-helper 1 (Th1) cytokines interferon- γ (IFN- γ) and IL-12. The two responses act in opposition to each other. The cytokine response governing

IgE production could be due either to a decreased Th1 response or to a raised Th2 response.

Temporary remission of hyper-IgE syndrome has been observed following viral infection, which suggests that stimulation of the Th1 cytokines ameliorates disease (60). Several authors have shown a reduction in Th1 cytokines in hyper-IgE syndrome patients when compared with healthy controls. Decreased production of IFN- γ by T cells has been demonstrated in four hyper-IgE syndrome patients (61). These four also showed fewer IFN- γ and tumour necrosis factor- α (TNF- α) producing T-cell clones in their peripheral blood populations. Flow cytometry and intracellular cytokine analysis have shown a decreased ratio of IFN- γ staining cells in the circulating T-cell pool (13). Further support for this argument comes from the recent findings of Borges et al. (62). Using the T cells from 10 patients with hyper-IgE syndrome, they found that there was a significant reduction in the amount of IFN- γ secreted from T cells when stimulated with heat-killed staphylococci. This was partially alleviated by stimulation with IL-12. Proliferation assays were also poorer in hyper-IgE syndrome patients compared with controls.

Whilst the Th1 response appears to be reduced, the Th2 response does not appear to be over-active. Rodriguez et al. found that there was no difference in IL-4 production between hyper-IgE syndrome patients and controls (63). In this study only asthmatic patients showed an increase in IL-4 production. However, IgE production in hyper-IgE syndrome may be regulated predominantly by IL-13 (64).

B-cell function in the hyper-IgE syndrome has also been explored. It was initially thought that IgE synthesis by B cells was not under direct cytokine control (59, 65). The addition of IL-4 to B-cell culture does not augment IgE synthesis *in vitro*, suggesting that B cells in hyper-IgE syndrome are already fully stimulated (66). However, antibodies to the Th2 cytokines (IL-4, IL-13 and IL-6) stop spontaneous IgE production *in vitro* as do antibodies against the IL-4 receptor (67). This shows that IgE synthesis remains IL-4/IL-13 receptor pathway dependent. In contrast to the poor responses to IL-4 *in vitro*, the same study showed that the Th1 cytokines IFN- γ and IL-12 dramatically reduce IgE synthesis, as does IL-8 (67). Whilst B-cell production of IgE may be maximal, catabolism may also be impaired. Using radiolabelled IgE, the catabolism of IgE was decreased in hyper-IgE syndrome and severe atopy (68).

Hyper-IgE syndrome should be distinguished as a clinical entity distinct from severe eczema or atopy. In the studies quoted above, many used atopic patients as a comparison in addition to a healthy control group. In spite of this, the nature of the immunopathological differences between atopy and hyper-IgE syndrome remains unclear. It seems that Th2-mediated IgE synthesis is a common pathway for both diseases. Our current understanding of the immune system has failed to provide a satisfactory explanation of the observed clinical manifestations of the hyper-IgE syndrome. When the true nature of the underlying defect is known it is likely that it will teach us something fundamental about how the immune system works in health as well as in disease. This in turn will lead to improved treatment.

Treatment

Prophylactic antibiotics, skin care and the prompt treatment of infection have been the mainstay of the treatment of hyper-IgE syndrome. The dermatitis will often improve with prophylactic antibiotics alone, unlike atopic dermatitis (69). Surgical intervention may be required for the incision and drainage of abscesses. Pneumonias are frequently complicated and surgical or chest tube drainage is often required. Donabedian and Gallin described 13 patients of whom seven had required chest tube drainage during infection and six later required lobectomy (10).

Several immunomodulatory therapies have been tried with variable clinical and laboratory success. The majority of these are as therapeutic trials reported as single cases or small anecdotal series of patients. The same therapies are also of use in the treatment of atopic disease, especially those with severe atopic dermatitis. The joint mechanisms of action occur by pharmacological intervention on the shared common pathways of T-cell phenotype shift from Th2 to Th1, on the action of IgE, or on neutrophil function.

The histamine receptor-2 (H2) antagonist, cimetidine, has been shown to reverse the hyper-IgE syndrome neutrophil chemotactic defect *in vitro* (51). The single patient in this study also showed a clinical improvement on treatment. Neutrophil chemotaxis was variable over time but improved on treatment and remained good on discontinuation of cimetidine in spite of a clinical relapse. Thomson and Kumararatne reported that H2 antagonists have been of benefit in the treatment of seven

patients with hyper-IgE syndrome, with or without the addition of an H1 antagonist (70).

Cromoglycate has been used with good clinical effect in a single patient with hyper-IgE syndrome (71). The dose used was 2 g orally per day in an underweight 7-year-old boy. The maximum recommended dose is 40 mg/kg/day in divided doses (72). No adverse effects were reported at this dose in this child.

Levamisole has been shown to be inferior to placebo in a blinded randomized trial with infection as a clinical end-point (73). The trial involved eight patients with hyper-IgE syndrome treated with levamisole at a dose similar to that used in the treatment of rheumatoid arthritis. Six courses of treatment were due to be given and each course was randomized so that each patient received three placebo and three levamisole courses during the trial. No significant difference in the occurrence of infection could be demonstrated between groups and so the trial was halted early. In fact, levamisole was demonstrated to be significantly inferior to placebo in preventing infection using an infection score as end-point. This is the only double-blind, placebo-controlled trial of a management intervention in hyper-IgE syndrome. It may be that the other treatments discussed here are equally ineffective and would not stand up to such experimental scrutiny.

Isotretinoin improved the dermatitis of a 15-year-old boy with hyper-IgE syndrome (74). It was used at a dose of 1 mg/kg/day over four months. Isotretinoin was instigated as the boy's skin became increasingly infected during puberty. There were no further abscesses in this patient and, apart from an initial deterioration, his eczema improved as was evidenced by a reduction of the potency of his topical steroids.

Cyclosporin A (CsA) was used in a 3-year-old boy with hyper-IgE syndrome (75). His skin cleared at a dose of 3 mg/kg/day over six months. On discontinuation the dermatitis recurred with infections. CsA was recommenced with a dramatic improvement in his clinical condition. During this period his serum IgE fell from 30 000 IU/ml to 500 IU/ml. CsA has also been used at 5 mg/kg/day in two patients with a clinical and laboratory response (76). No untoward side-effects were noted during the 18 months of treatment. The mechanism of action is unknown but may be due to a shift away from a Th2 response.

Interferon- γ has been shown *in vitro* to improve neutrophil chemotaxis in hyper-IgE syndrome following a dose-response curve (23). Five patients with hyper-IgE syndrome were treated over 2 weeks with a dose of 0.05 mg/m² three

times weekly, on alternate days, by subcutaneous injection (77). Serum IgE was significantly reduced in one patient and all patients showed reduction in peripheral blood mononuclear cell (PBMC) production of IgE. The dose was increased in the four non-responders to 0.1 mg/m² and again one patient's serum IgE dropped. No change in clinical status was observed but no infections occurred during treatment either. However, IFN- γ has been associated with the development of autoimmune thrombocytopenia when used in hyper-IgE syndrome (78). IFN- γ may also paradoxically increase serum IgE in hyper-IgE syndrome, prompting discontinuation of treatment (J. O. Warner, personal communication).

Interferon- α (IFN- α) has been used clinically (79). The single patient involved had severe allergy and eczema, probably incorrectly termed hyper-IgE syndrome. Not enough clinical information is supplied to make an accurate diagnosis from the account. Her eczema disappeared over a 4-week course at a dose of 3×10^6 U twice weekly. IgE levels also fell over this period. The eczema gradually returned but in a milder form following the discontinuation of treatment. IFN- α has not been shown to affect neutrophil chemotaxis *in vitro* (23). Another atopic patient with recurrent infection and food allergies has been shown to respond to dietary restriction (80). Again, this girl is not likely to be suffering from true Job's syndrome and the diagnoses of severe atopy and hyper-IgE syndrome have become confused.

High dose intravenous γ -globulin (IVIG), at a dose of 400 mg/kg/day for 5 days, has been used in two children with hyper-IgE syndrome and Kawasaki disease (81). Not only did the fever subside but the eczema also disappeared. The use of IVIG may have been enhanced by the Th1 response to Kawasaki disease in these children. Further treatment of another patient with hyper-IgE syndrome, but without Kawasaki, also showed clinical effect as it did in several children with atopic dermatitis. IgE levels and B-cell production of IgE and anti-staphylococcal IgE were shown to decrease after therapy.

Plasmapheresis has been effective in a 49-year-old woman with hyper-IgE syndrome (82). A course of five plasma exchanges with fresh frozen plasma was administered over 10 days. Following this the lady had an improvement in skin condition for two months and was free of infections for six months. Other reports have also shown benefit from this invasive approach (8, 83).

Bone marrow transplant provides the only hope of cure at present, albeit at high risk to the patient. There is a single case report of a 46-year-old man who developed a B-cell lymphoma that required a peripheral stem cell transplant (40). He had a history of hyper-IgE syndrome, with pneumonias, since childhood. Two of his four children were also affected with hyper-IgE syndrome. Total body irradiation preceded transplantation and, following this, he was maintained on prednisolone and CsA to prevent graft vs. host disease. Serum IgE returned to normal values following transplant and the symptoms of hyper-IgE syndrome also disappeared. Unfortunately, he died following an interstitial pneumonitis. This may have been predisposed to by pretransplant lung damage.

Summary

Hyper-IgE syndrome is a rare, serious primary immunodeficiency of unknown etiology. It is associated with a range of skeletal abnormalities as is seen in other immunodeficiency syndromes. It has variable features and there is no single laboratory or clinical investigation that can secure the diagnosis. Treatment is supportive and prophylactic skin care and antibiotics are the most helpful interventions. Recent advances in the understanding of the genetics and immunology of this condition may elucidate the responsible gene, genes or chromosomal deletion. This in turn will provide hope for new treatment strategies in the long term.

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