

Cyclosporin for Treatment of Hyperimmunoglobulin E Syndrome: A Case Report

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Abstract

Hyperimmunoglobulin E syndrome (HIES) is a rare primary immunodeficiency characterized by elevated serum IgE, dermatitis, and recurrent skin and lung infections. The pathogenesis of this disease is still unknown. There is no definitive therapy for HIES, the treatment is mainly for prevention and management of infections. Immunoglobulin supplementation or low dose cyclosporine has been reported helpful. We present a case of 16-month-old boy with hyperimmunoglobulin E syndrome. He was administered with 3 grams (300 mg/kgBW) of intravenous immunoglobulin. After IVIG administration the papules decreased in number or partially resolve but fever and itchy rash still persisted. The patient then received cyclosporine 2x25mg/day (5mg/kgBW/day) for 6 months. There was improvement in clinical manifestations after 1 month therapy with cyclosporine, although IgE level did not decreased. Two years after treatment, the patient is still in good condition.

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INTRODUCTION

Hyperimmunoglobulin E syndrome (HIE) is a rare primary immune deficiency, characterized by skin rash, recurrent infections of the skin and lungs, as well as elevated levels of serum immunoglobulin E (IgE). HIE syndrome is mostly an autosomal dominant disorder caused by mutations

in signal transducer and activator of transcription (STAT3) but other more rare autosomal recessive form also exist. HIE syndrome causes more susceptible to infection.

The clinical features of HIE syndrome is highly variable and can involve skin, lung, bone and blood

vessel. We must be vigilant against any of the symptoms which might be a clinical manifestation of HIE syndrome. Until now, there has been neither definitive diagnosis investigation nor therapy. The purpose of the treatment is to eradicate the infection, reduce morbidity and prevent complications. The management includes antibiotics, antifungal, skin care, intra- venous immunoglobulin therapy, and cyclosporine for cases that do not response adequately to previous treatment.

CASE REPORT

A boy aged 1 year and 4 months came to the Pediatrics Department of Cipto Mangun- kusumo Hospital, Jakarta, with a chief complaint of multiple hives or papule all over body since one month before admission.

Reddish skin papules aroused, initially on the back and then spread to the feet, hands and face which were later darkened and accompanied with itchy and fever. Patient also often experienced fever, runny nose and cough. No recurrent stomatitis or gastrointestinal symptoms were found. The patient had never experienced such pain before. No previous history of serious illness or prolonged drug use. No family member had experience similar illness. There was no history of atopic in patient and family.

He is a second child of two brothers. The pregnancy history was unremarkable. He had complete basic immunization. Growth and development are normal.

General physical examination was unremarkable except for erythematous papule, multiple and discrete throughout the body

Laboratory investigations showed hemo- globin, haematocrit, platelets remains normal. Leukocytes slightly increase (14700/uL), with the normal differential count. Aspartate aminotransferase and alanin aminotransferase level were normal. Serum urea and creatinine were normal. The level of IgE was advanced increase (1893 IU/L), level of IgG was advanced increase (1617 mg/dL). Specific immunoglobulin were within normal limits, CD4 and CD8 were normal, level of C3 and C4 were normal, ESR (22 mu/hr) was increase. Based on those findings patient was diagnosed with hyperimmunoglobulin E syndrome (Job's syndrome).

Patient was treated with antibiotic clin- damycin and cetirizine for the itchy, but showed no adequate response Then, patient was treated with 3 grams of intravenous immunoglobulin therapy (300mg/kg) in 3 consecutive dose, cetirizine 2x3 mg per oral and skin moisturizer.

After administration of the first immuno- globulin papules were diminished and dry- ing but itchy still persist. Patient was also still often experience recurrent fever accom- panied by cough and cold which were improved with antibiotics. The second immu noglobulin therapy was given one month later with the same dose. Papules diminished and dried up after two weeks by the time of second immunoglobulin



Figure 1. A boy aged 1 year and 4 months with multiple hives or papule all over body since one month before admission



Figure 2. A boy aged 1 year and 4 months after given cyclosporine, the multiple hives are decreased

administration. Patient was still often experience fever. The administration of two dose IVIG in one month interval resulted in partial response (papules improved but fever and itchy persisted). We decided to give cyclosporine 2x25 mg (5mg/kg/day) for 6 months. Fever and itchy disappeared, and the patient showed clinical improvement. Review of complete blood count and renal function showed normal results. For all the parameter that previously been examined remains normal. Only IgE level remain increase (IgE 2867 u/mL). Two years, undergoing treatment, the patient is still in good condition.

DISCUSSION

Hyperimmunoglobulin E syndrome (HIE) is a rare primary immune deficiency occurs, marked skin rashes, recurrent infections of the skin and lungs accompanied by increased levels of immunoglobulin E serum. HIE syndrome is also known as Job's syndrome. These disorders may be autosomal dominant caused by mutations in signal transducer and activator of transcription (STAT3) or autosomal recessive.¹

Job's syndrome was first recognized in 1966 by David, et al in one case with a rash on the skin and lung infection. In 1972 Buckley, et al reported similar cases with increased serum IgE that is known as a hyperimmunoglobulin E syndrome. HIE syndrome is characterized by recurrent abscesses due to staphylococcal sp, dermatitis, pneumonia, hyperextensibility, and increased of IgE. Currently, HIE syndrome is autosomal dominant (AD HIE) is known

as a multisystem disorder with a variety of connective tissue disorders, bone, and vascular. Mutations in the signal transducer and activator of transcription 3 play a role in most cases of HIE AD.

While the autosomal recessive HIE syndrome (AR HIE) is a clinical disorder characterized by eczema, recurrent skin and lung infections accompanied by increased serum IgE, which is susceptible to viral infection accompanied by CNS involvement. Pathogenesis of both clinical manifestations and immunological abnormalities are still not fully understood. HIE syndrome is a rare disease. There are only about 250 cases have been published. There is no gender or ethnic predilection. HIE syndrome usually occurs during infancy, but the diagnosis is often delayed until childhood or even up to adult.^{6,7} Genetic basis of HIE syndrome remains unclear, it is generally sporadic. There are cases of two siblings with parents who are not affected by this disorder that is estimated to be autosomal recessive, but some other symptoms cases show autosomal dominant⁸. In our case, there is no family history of similar complaints, so it is likely to be sporadic.

Immunodeficiency disorder is caused by genetic mutations that can cause excessive stimulation or low stimulation of the immune system, making it easy to get bacterial and fungal infections. Patients may survive or suffer serious complications due to the infection. Job's syndrome causes the immune system becomes highly sensitive to microbial attack.

Patients often experience recurrent infections such as dermatitis and pneumonia.



Figure 3. A boy after two years therapy, the multiple hives are dismissed, remains scar and hyper pigmentation lesion

Steven M. Holland, et al in 2009, revealed that there is a protein that causes the body increase the production of leukocytes, enhance immune system, and improve the ability to kill microbes. This protein is known as STAT (signal transducer and activator of transcription). STAT proteins help the immune system to stop the invasion of pathogens. In this study it was found that genetic mutations occur in STAT3 protein and cause the Job's Syndrome.⁹

Atopic dermatitis HIE syndrome usually occurs in the first week of life in the form of a rash in neonates. Pustule rash is often arising in the head and face in the form of neonatal acne and eosinophilic dermatitis. Eczema rash can become infected with *Staphylococcus aureus*. Other complications that can occur is pneumonia. Recurrent pyogenic pneumonia usually occurs in early childhood, with purulent sputum, but is rarely accompanied by systemic manifestations such as fever.

The main pathogens that usually cause infections are *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. In the healing phase is usually accompanied by pneumatocele pneumonia and bronchiectasis. These structural abnormalities are usually followed by fungal infections and gram-negative bacteria, as a major cause of mortality and morbidity in HIE syndrome. HIE syndrome is distinguished from other immunodeficiency based on the immunologic feature. Typical symptoms of HIE syndrome generally occurs in childhood and

adolescence, it is marked with an asymmetric face, broad fleshy nose, and porous skin.²

Complications occur in blood vessels and skeletal systems. Skeletal fracture is a complication that occurs due to minimal trauma, osteopenia, hyperextensibility, scoliosis, and degenerative joint disease is common. Vascular abnormalities may occur, but usually asymptomatic.²

Grimbacher, et al, in cohort research for over 20 years of getting abnormalities in the teeth, bones, and connective tissue in patients with HIE, concluded that this syndrome include abnormalities of multiple organs. The frequent of fracture describe high levels of cytokines that mediate bone reabsorption. Bone fragility result from reduced bone mineralization or bone abnormalities.⁸

Another study by Chamlin, et al in 2002 of eight children with HIE syndrome who had early symptoms of papule-pustule eruption, especially on the face and head. The diagnosis of HIE syndrome is established 18 months later after the onset of papule pustule eruption. This skin disorder can be helpful for early diagnosis so that proper management for the patient can be immediately given.¹⁰ In our case, the initial symptoms are recurrent skin infections with itching and fever since one month before hospital admission. Other complaints, such as cough and fever recurring colds, indicate the presence of immunodeficiency in patients. The elevated levels of immunoglobulin E, prove the diagnosis of HIE syndrome in patients. Other clinical

manifestations such as pulmonary abnormalities, teeth, and bones did not arise in our patients. It is likely due to the patient was receiving a new treatment. The age of patient is still 1 year and 4 months. Manifestations in other organs usually occur with age, especially if the diagnosis is established during adolescence or adulthood when many complications have arisen. So the likelihood of complications in other organs in our patient still needed to watch out.

Significant laboratory abnormalities were eosinophilia and increased of serum IgE. Serum immunoglobulin E increased to more than 2000 IU / mL, but can be decreased and reached normal adulthood. The levels of IgA, IgG, and IgM are usually normal. Leukocytes are usually normal, but on the circumstances of infection can occur leukocytosis and increased CRP but not high enough.² In our case, we found elevated levels of IgE, IgG, IgA and IgM levels while still within normal limits.

HIE syndrome has no definitive therapy. The goal of therapy in HIE syndrome is to eradicate the infection, reduce morbidity, and prevent complications.⁶ include providing antimicrobial therapy and skin care, and intravenous immunoglobulin and cyclosporin^{1, 11}. Antibiotics usually are given, like nafcillin, oxacillin, ampicillin, vancomycin, cefazolin, and cotrimoxazole. Antifungals such as fluconazole and ketoconazole works by affecting the metabolism of RNA and DNA as well as intracellular accumulation of toxic peroxidation of fungal cell.⁵

Intravenous immunoglobulin therapy (IVIG) was first recognized in 1952 as a therapy of primary immunodeficiency. In 1981, Paul Imbach got the improvement of immunity in patients with thrombocytopenia who received IVIG therapy. Since that time IVIG therapy as a choice for a variety of autoimmune and acute inflammatory diseases.¹² Food and Drug Administration (FDA) has approved the use of IVIG for primary immunodeficiency conditions, ITP, Kawasaki disease, bone marrow transplantation, chronic B cell leukemia myeloblastic, and HIV in children.¹⁰ Today, IVIG has been a therapeutic option for patients with primary immunodeficiency to prevent recurrent infections are administered at a dose of

200-400 mg / kg every 3 weeks.

While the administration of immunoglobulin as immunomodulators using high-dose (2 g / kg).^{13,14} Mechanism of action of IVIG depends on the dose and the pathogenesis of underlying disease. The study by Ammann et al in 1972 concluded that there was more obvious clinical improvement in primary immunodeficiency by administering small doses of IVIG (150 mg / kg). Roifman (1987), which compares with a dose of IVIG mg/kgBB 600 and 200 mg / kg in patients with primary immunodeficiency, have decreased the frequency of infections and improvement of spirometry function by administering doses of 600 mg/kgBB.¹³⁻¹⁵ Another study conducted by Hajime Kimata in 1995 concluded that IVIG therapy is effective for severe dermatitis in HIE syndrome and atopic dermatitis. Immunoglobulin is also able to decrease IgE production both in vivo and in vitro,¹⁶ although this remains controversial. Research conducted by Wakim, et al in 1998 concluded that IVIG did not significantly reduce levels of IgE.¹⁷ In our case, the patient received IVIG at a dose of 300 mg / kg, two times with an interval of one month. Improvement occurred in patients with papules, papules on the skin that began to diminish and dry, although there is no impairment in laboratory IgE levels.

In the case of HIE syndrome who do not respond well to existing therapies, can be given cyclosporine at a dose of 2.5 to 5 mg/kg/day for 6 months or more. This therapy usually responds well to skin infections and lung infections, as well as the adverse effect has not been reported.³ Kitai, et al (1996), Etzioni, et al (1997), Tamas, et al (2008), showed a clinical improvement and decreased levels of IgE in HIE syndrome patients receiving cyclosporine therapy A.¹⁸⁻²⁰ Our patient had received IVIG two times and experienced clinical improvement of skin disorder is reduced, but the patient still feels itchy and often experience fever.

After cyclosporine therapy 2x25 mg daily for six months, one month after administration of cyclosporine skin disorders have disappeared and blackish scars still remain. A Complaint of itching and fever that has

been undergone by the patient is gone. The prognosis of patients with HIE syndrome varies depending on the time of diagnosis and the incidence of complications. Until now there has been many cases, report and no studies of long-term prognosis in patients with HIE syndrome. The prognosis in these patients is much better because HIE syndrome diagnosis could be established at an early stage before the onset of complications. Nevertheless, the observation of the occurrence of complications later in life still needs to be done.

CONCLUSION

A case of a 16-month-old boy with hyperimmunoglobulin E (HIE) syndrome has been reported. The diagnosis of HIE syndrome based on patient's history, physical examination, and laboratory findings. The patient was admitted with generalized papul on the whole body that accompanied with recurrent fever and cough. The laboratory findings revealed increased of immunoglobulin E level. Treatment of HIE syndrome remains supportive, including treatment of dermatitis and prevention of infection. Intravenous immunoglobulin showed no satisfying improvement in this patient, therefore he was received cyclosporin for six month. In further evaluation, immunosupresant therapy using cyclosporin showed a better clinical improvement. Understanding of the diverse clinical manifestations of this rare condition will hopefully help the pediatrician able to early diagnosis HIE syndrome. A small dose of cyclosporin A is beneficial in patients with HIE syndrome. It should be considered in severe cases where other therapeutic modalities have failed.

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