

## Hyper-IgM syndrome: a case report

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Hyperimmunoglobulin M syndrome is a rare primary immunodeficiency disorder. We report a case of a 6-month-old boy who suffered from developmental delays, frequent respiratory tract infection, and unusual fungal and bacterial infection. X-linked hyperimmunoglobulin M syndrome was ultimately diagnosed with decreasing immunoglobulin-G, A, and E (immunoglobulin G = 51.3 mg/dL, immunoglobulin A = 8.32 mg/dL, immunoglobulin E <17.5 mg/dL), elevating immunoglobulin M (immunoglobulin M = 140 mg/dL), and decreasing T-cell expression of the CD40 ligand over flow cytometry. Seizure episodes and hypotonia developed with greater signal intensity at the putamen in a brain magnetic resonance imaging, which is compatible with hypoxic ischemic encephalopathy. This is the youngest proven case of hyper-IgM syndrome in Taiwan ever reported.

**Key words:** CD40 ligand, hyperimmunoglobulin M syndrome, hypoxic ischemic encephalopathy

Immunodeficiency with hyperimmunoglobulin M (IgM) is a rare genetic disorder characterized by low levels of serum IgG, IgE, and IgA, with normal or high IgM levels and recurrent opportunistic infections with encapsulated bacteria, *Pneumocystis carinii*, and *Cryptosporidium*. Genetic heterogeneity is indicated by the occurrence of X-linked and autosomal recessive variants. The mutation is located at Xq26.3-27, a gene encoding for the CD40 ligand. The CD40L is a type II integral transmembrane glycoprotein, expressed mainly by activated CD4 sup + T-lymphocytes. Interactions between activated CD4 sup + T-cells expressing the CD40L and B-lymphocytes serve as fundamental membrane signals for B-cell growth and differentiation. In the absence of an appropriate CD40-CD40L interaction, activated CD4<sup>+</sup> T-cells fail to drive the isotype switching of IgG, IgA, and IgE production and the memory B-cell generation in response to T-cell-dependent antigens, as well as the formation of germinal centers. However, their ability to produce IgM is preserved [1]. Herein we present a case of hyperimmunoglobulin M syndrome with hypoxic ischemic encephalopathy, and discuss the differential diagnosis and its association with seizure episodes and hypoxic ischemic encephalopathy.

### Case Report

A 6-month-old boy was born to a healthy mother

without any perinatal insult or infectious episodes. At 4 months old, the child endured frequent respiratory tract infections, choking, and poor weight gain. Because of dyspnea with lip cyanosis, he was brought to our emergency services unit, where leukocytosis with predominant lymphocytes and bilateral reticular and granular infiltration on the chest x-ray were found. Under the impression of interstitial pneumonitis, viral serology studies, throat swabs, and sputum *Mycobacterium tuberculosis* cultures were performed without subjective findings. He was emergently intubated because of respiratory distress; methylprednisolone was prescribed under the impression of acute respiratory distress syndrome for whiteouts noted in the follow-up chest x-ray. Bronchoscope examination showed a whitish exudate coating the trachea and the bilateral bronchial mucosa. Bronchial lavage fluid yielded macrophages and neutrophils. Cytological study of the alveolar fluid delineated histiocytes and lymphocytes predominating and the bronchial lavage exudate culture grew *Candida albicans* and *Pseudomonas*.

Because of unusual and poorly controlled infections, immunological studies were performed, which revealed decreased immunoglobulin G (IgG) and elevated immunoglobulin M (IgM). IgG = 51.30 mg/dL (reference, 427 ± 186), IgA = 8.32 mg/dL (28 ± 18), IgM = 140 mg/dL (43 ± 17), IgE <17.5 mg/dL. T-cell level was 78%, B-cell level was 21%, and NK cell level was 0.7%, CD3+CD8<sup>+</sup> was 18%, CD4<sup>+</sup> T-cell was 57%, naïve cell was 52%, and memory cell was 5% over the lymphocyte subset. Mitogen for T-lymphocyte

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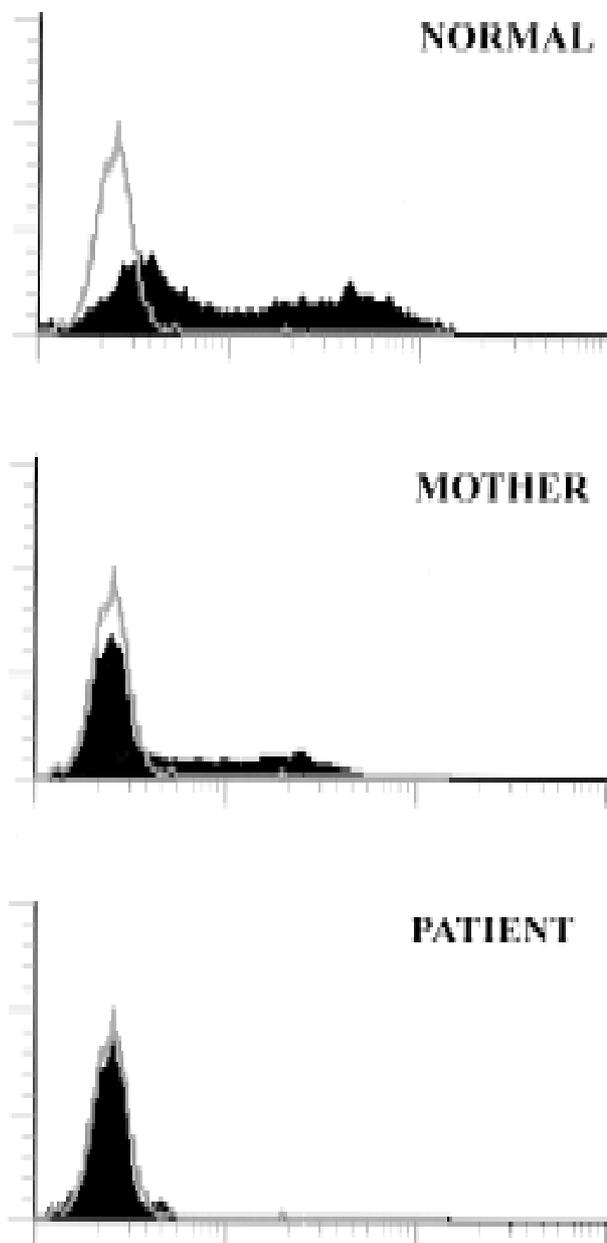
proliferation revealed PHA:3425/514 (SI = 6.7), PWM: 28524/514 (SI = 55). The expression of CD40L was measured by flow cytometry on the surface of activated CD4 T-cells and revealed a severe reduction compared with the normal control and his mother. T-cells ( $10^7$  cells/mL) were stimulated with PMA (20 ng/mL) plus calcium ionophore (1  $\mu$ M) for 10 h and labeled with isotype control (IgG1-PE), CD45-PC5, CD4-FITC, or CD40L-PE 10  $\mu$ L. Labeled cells were analyzed on a FAC scan (Fig. 1). Under suspicion of hyper-IgM syndrome, intravenous immunoglobulin G (1 g/kg) was prescribed.

Follow-up immunological workups 1 month later showed IgG = 256 mg/dL ( $427 \pm 186$ ), IgA <24 mg/dL ( $28 \pm 18$ ), IgM = 46.5 mg/dL ( $43 \pm 17$ ). Unfortunately, an episode of generalized seizure and massive gastrointestinal tract bleeding developed afterwards. Cerebrospinal fluid (CSF) studies revealed protein at 22.6 mg%, glucose at 108 mg%, and no growth in the bacterial and viral cultures, without strong evidence of infection. Electrical encephalography showed diffuse cortical dysfunction without epileptiform discharge. Because of hypotonia, poor head control, rigidity of the four limbs, and seizure, a brain magnetic resonance imaging (MRI) was arranged. This revealed an increased density over the bilateral ganglions over T2-weighted images compatible with hypoxic ischemic encephalopathy (Fig. 2). After rehabilitation, he was discharged after 3 weeks of hospitalization. No seizure was found since.

## Discussion

Hyper-IgM syndrome is a rare immunodeficiency formerly classified as a B-cell defect. However, B-cells with this disease are capable of synthesizing not only IgM but also IgG and IgA after being co-cultured with a switch T-cell line. This indicates that the defect is of T-cell lineage. The frequent presence of lymphoid hyperplasia in XHIM often distracts a diagnosis away from immunodeficiency, until recurrent opportunistic infections developed in the first or second year of life [1].

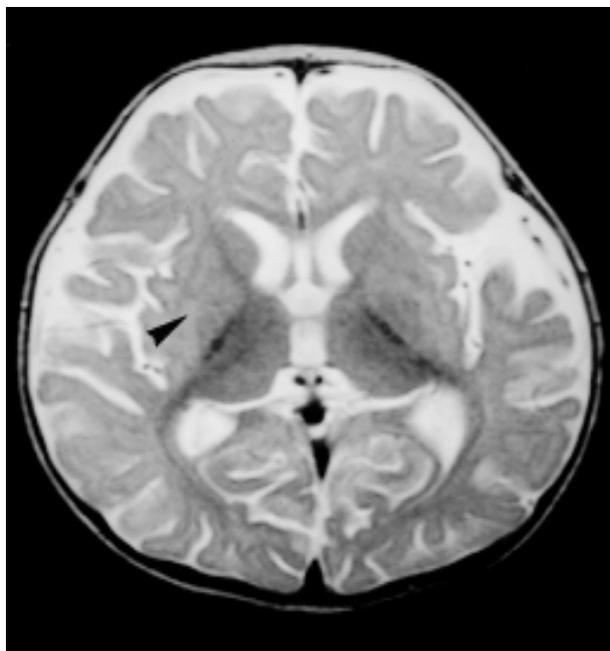
X-linked agammaglobulinemia and hyper-IgM syndrome were initially impressed in our case quite early – at 6 months old. In contrast to X-linked agammaglobulinemia, XHIM patients have a normal number of circulating B-lymphocytes, which express IgM or IgD, but no other isotypes on the cell surface [2]. In addition, since primary or secondary immunodeficiencies with reduced numbers of CD4+ T-cells may also have reduced CD154 expression, the expression of CD40L on activated CD4+ lymphocytes



**Fig.1.** Representative flow cytometry histograms of CD40L expression on *in vivo* activated T-cells obtained from a healthy individual (NORMAL), XHIM carrier (MOTHER), and XHIM patient (PATIENT). X-axis represents log fluorescence intensity of CD 40L; Y-axis represents CD4+ T cell counts. The percentage of CD4 gated T-lymphocytes expressing the CD40L after activation with PMA and ionophore. Black-filled histograms represent the activated cells; open histograms represent the *in vitro* non-stimulated cells (control).

might provide more information for the diagnosis of hyper-IgM syndrome [2].

Another interesting presentation is that this patient suffered developmental delays and seizure episodes after admission. Levy *et al* [3] reported 56 patients with



**Fig. 2.** Brain MRI without contrast (T2WI) axial section shows: increased signal intensity at the bilateral basal ganglion (arrowhead) compatible with hypoxic ischemic encephalopathy.

X-linked hyper-IgM syndrome and 7 patients with neurological problems. In this patient, CSF studies failed to identify a causative pathogen, therefore, CNS infection was not likely. It has been suggested that antiphospholipid antibodies are associated with increase risk of thrombosis, and should be systematically investigated in juvenile ischemic stroke cases of unknown etiology [4]. The obtained results demonstrated that the mean levels of IgA and IgM and the total proteins were higher in the cerebrospinal fluid and that the value of IgG was unchanged [5]. Therefore, elevated IgM in the CSF may somehow relate to hypoxic insults or seizures. Unfortunately, we failed to perform IgM levels in the CSF of this patient.

Plasmaphoresis to decrease IgM is supposed to be lower in acute neurological events [6]. Concerning immunodeficiency related developmental delays, B-cell lineage immunodeficiency, selective IgG2 subclass deficiency, and adenosine deaminase-defective severe combined immunodeficiency have been reported [7-9], but no one has ever reported any association with hyper-IgM syndrome. The developmental delays in this patient might be related to hyper-IgM syndrome or may simply be coincidental neurological problems: hypoxic ischemic encephalopathy caused by a hypoxic event due to choking, respiratory distress, or intubation; anemia due to massive gastrointestinal bleeding and

shock; or an unidentified perinatal insult. The seizure episodes were assumed to be associated with hypoxic ischemic encephalopathy or simply the complication of IVIG infusion.

After one course of IVIG infusion, the ratio of IgM and IgG was reversed in this patient. It has been reported that in 50 XHIM patients who received IVIG regularly, serum IgM levels decreased in 5 subjects and became normal in 9 of 26 patients who had elevated serum levels before the start of IVIG infusions [3]. However, IVIG infusion was palliative. Only successful bone marrow transplantation provided a cure [10]. Palliative IVIG infusion was administered as the major treatment in this patient because there were no HLA-matched family donors available. The boy has led a healthy life for 1 year now without severe infection after regular IVIG infusion.

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