A delayed diagnosis of X-linked hyper IgM syndrome complicated with toxoplastic encephalitis in a child
A case report and literature review
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Abstract
Introduction: The X-linked hyper-immunoglobulin M syndrome (XHIGM) is an uncommon primary combined immunodeficiency disease caused by CD40L gene mutations. A delayed or missed diagnosis of XHIGM is common and concerning, owing to atypical immunoglobulin profile and phenotype of some patients, low recognition, and limited knowledge of clinicians on XHIGM in some underdeveloped areas. Opportunistic infections are a prominent clinical feature of XHIGM. However, toxoplasma encephalitis occurs sporadically and is extremely rare in patients with XHIGM.

Diagnostic and therapeutic procedure: A 2 years and 10 months’ old male suffered from 3 times of serious infection since 1 year and 4 months of age. Although with history of recurrent respiratory infections, protracted diarrhea, persistent or intermittent neutropenia accompanied with oral ulcer, and a typical immunoglobulin profile during his second disease attack, the consideration of XHIGM was still completely ignored because of our low recognition and limited knowledge of this disorder. The diagnosis of XHIGM was ultimately confirmed by detection of elevated serum IgM concentration, decreased serum IgG and IgE concentration, and identification of a mutation c.654C>A (p.C218X) in CD40L gene. Given clinical manifestation of lethargy, uncontrollable somnolence and ataxia, a cat/dog exposure history, positive serum Toxoplasma gondii (T gondii) IgM, positive cerebrospinal fluid T gondii PCR results, and typical characteristics of brain magnetic resonance imaging as multiple rings liked nodules lesions in bilateral cerebral hemisphere cortex, bilateral basal ganglia, and dorsal thalamus, the diagnosis of toxoplasemic encephalitis was considered during his third disease attack. Thereafter, oral administration of sulfadiazine and azithromycin, intravenous immunoglobulin, and subcutaneous injection of G-CSF were initiated. Regrettably, the patient abandoned the treatment because of economic factor and died 3 months after discharge.

Conclusions: A more thorough clinical history and some features like recurrent respiratory infections, protracted diarrhea, and persistent or intermittent neutropenia accompanied with oral ulcer could increase clinical suspicion of XHIGM. Cerebral toxoplasmosis is rare in patients with XHIGM, but still should be considered. The present study firstly reported a delayed diagnosed case of XHIGM with CD40L gene c.654C>A (p.C218X) mutant complicated with toxoplasma encephalitis in Chinese population, which highlighted the importance of CD40-CD40L interaction in cell-mediated immunity against T gondii.

Abbreviations: CD40L = CD40 ligand, CNS = central nervous system, CRP = C reaction protein, G-CSF = granulocyte colony-stimulating factor, HCT = hematopoietic cell transplantation, HIGM = hyper-immunoglobulin M syndrome, P carinii = Pneumocystis carinii, T gondii = Toxoplasma gondii, XHIGM = X-linked hyper-immunoglobulin M syndrome.

Keywords: CD40 ligand, cerebral toxoplasmosis, child, delayed diagnosis, X-linked hyper-IgM syndrome
1. Introduction

The X-linked hyper-immunoglobulin M syndrome (XHIGM; HIGM1; OMIM: 308230) is an uncommon primary combined immunodeficiency disease caused by the mutations of CD40 ligand (CD40L) gene. With a frequency of about 2:1,000,000, it accounts for 65%~70% of all forms HIGM[1] and results from defective CD40-CD40L signaling pathway characterized as normal or elevated serum levels of IgM, low serum levels of IgG, IgA, and IgE, and defective T-cell function.[2] Overall, the prognosis of patients with XHIGM was relatively poor, with an average of 20% survival by age 25 years. However, with early diagnosis and subsequent supportive treatment (e.g., regular treatment with intravenous immunoglobulin, prevention of opportunistic infections such as Pneumocystis with trimethoprim-sulfamethoxazole) and even corrective therapy (hematoopoietic cell transplantation), those patients have a much better chance to survive.[3,4] Unfortunately, owing to atypical immunoglobulin profile and phenotype of some patients in early disease stage, low recognition and limited knowledge of clinicians on XHIGM in some underdeveloped areas, a delayed or missed diagnosis of XHIGM is common and concerning, even for those with positive family history, which might lead to recurrent opportunistic infections, malignancy occurrence, and even death.[5-6]

Pneumonia was the most common infection in patients with XHIGM, followed by recurrent sinussitis, otitis, oral ulcer, and protracted diarrhea. Central nervous system (CNS) infection was relatively uncommon, with an incidence of 5% to 10% in different case series.[3,7] Opportunistic infections were a prominent clinical manifestation of XHIGM. CNS infections with Histoplasma capsulatum, Cryptococccneo-formans, cytomegalovirus, echovirus, and Mycobacterium bovis have been reported in patients with XHIGM.[4] However, toxoplasma encephalitis, predominantly in those with AIDS and in cardiac transplants patients,[8,9] occurs sporadically and is extremely rare in patients with XHIGM. Here, we reported a delayed diagnosed case of XHIGM with CD40L gene c.654C>A (p.C218X) mutant, who had recurrent severe infections for almost 3 times before and finally died of toxoplasma encephalitis, aiming to share some experience and improve the recognition and prompt diagnosis of XHIGM for pediatric clinicians, and highlight the importance of the CD40-CD40L system in the defense against toxoplasmal infection.

2. Case report

The patient was a 2 years and 10 months old male. He was firstly admitted into local hospital because of diarrhea and lethargy 1 month before transferring to our hospital. With fluid therapy for 1 week, the symptoms of diarrhea remarkably relieved. However, his mental status became worse and onset with fever and hypoglia. Even worse, those situations did not turn better and abnormal gait and ataxia gradually occurred to him 2 weeks later. Then, he was transferred to our hospital because several patch-shaped hypointense lesions with surrounding edema in bilateral basal ganglia and frontal lobe were noted on the brain CT scan. On arrival, he was lethargic, afibrile, had no bradycardia, no irregular breath, and no hypoxia. Abnormal gait was noted and the Romberg sign was positive. Meningeal irritation sign and Babinski sign were negative. No other positive findings were identified by physical examination. Any history of drugs or poisons taken and abnormal growth or mental retardation before symptoms onset was denied by his parents. However, a history of recurrent infections was recorded and he has been hospitalized in our hospital for 2 times because of serious infections (Table 1). He was admitted for the first attack because of prolonged fever, recurrent oral ulcer, otitis media, protracted diarrhea, and peritonitis at the age of 16 months. For the second attack, his symptom was more serious and had been admitted into our pediatric intense care unit (PICU) because of diarrhea, severe pneumonia, and acute respiratory distress syndrome, and was aged 23 months.

For the auxiliary examination, neutropenia (0.16 × 10^9 cells/L) was detected in blood routine test. However, C reaction protein (CRP), erythrocyte sedimentation rate, procalcitonin, liver function, renal function, blood creatase levels, blood gas analysis, blood glucose, blood ammonia, blood fat, autoantibody, anti-neutrophil cytoplasmic antibodies, and thyroid function were unremarkable. Cerebrospinal fluid (CSF) examination was also normal. CMV-IgM, HSV-IgM, RV-IgM, EBV-IgM, JEV-IgM, EV71 antigen, coxsackie virus antigen, mycoplasma IgM, TPPA, T-spot, PPD skin test, fungal G test, and GM test were negative. Notably, a positive serum Toxoplasma gondii (T gondii) IgM was found. Brain vascular magnetic resonance imaging (MRI) did not reveal any abnormal findings. However, multiple rings liked nodules lesions in bilateral cerebral hemisphere cortex, bilateral basal ganglia, and dorsal thalamus were detected on brain MRI with enhancement (Fig. 1). Given the characteristic features of the brain MRI, positive serum T gondii IgM and a cat/dog exposure history, the diagnosis of toxoplasmal encephalitis was suspected. Furthermore, PCR amplification of T gondii in the CSF was performed. Encouragingly, the result was positive and confirmed our diagnosis. Ophthalmic examination was done thereafter and no positive findings were revealed.

Given the diagnosis of toxoplasmal encephalitis and the history of recurrent infection, an increased clinical suspicion of

| Table 1 |
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| Clinical manifestations of this patient for 3 times attack. |

| Duration of the attack, days | Pathogen | Clinical Presentation | Treatment |
| --- | --- | --- | --- |
| 1st | None | Oral ulcer, otitis media, diarrhea, peritonitis, sepsis, URI | Meropenem, G-CSF |
| 2nd | S pneumoniae, IVB | Diarrhea, Severe pneumonia, respiratory failure | Mechanical assisted ventilation, Meropenem, Vancomycin, Micafungin, IVG |
| 3rd | Toxoplasma gondii | Lethargy, diarrhea, hypoglia, ataxia, Cerebral toxoplasmosis | SMZ, Azithromycin, G-CSF, IVG |

G-CSF = granulocyte colony-stimulating factor, IVB = influenza B virus, IVG = intravenous Immunoglobulin, S pneumoniae = Streptococcus pneumonia, SMZ = sulfamethoxazole, URI = upper respiratory infection.
immunodeficiency was initiated. Negative serum HIV antibody ruled out the possibility of HIV infection. Immediately, examinations regarding humoral and cellular immunity were done and elevated serum IgM concentration (1.78 g/L, normal range: 0.43–1.63 g/L), decreased serum IgG concentration (1.05 g/L, normal range: 3.41–19.6 g/L) and IgE concentration (<165 IU/ml), but normal serum IgA level (1.24 g/L, normal range: 0.19–2.2 g/L) were found. The lymphocyte counts and the percentage of different lymphocyte subsets including CD3/CD4/CD8/CD19 were generally normal, but with a reduced ratio of CD4/CD8 (0.6, normal range: 1.5–2.0). In light of those findings, the diagnosis of HIGM was highly suspected. Thereafter, we reviewed the results regarding humoral and cellular immunity during his previous 2 times of hospitalization (Table 2). His high IgM with normal IgG and IgA concentrations, detected during his first attack, were not characteristics for HIGM. However, with a typical immunoglobulin profile during his second severe attack, the possibility of HIGM was still completely ignored, which arose from our low recognition and limited knowledge of this disorder.

To confirm our suspicion, the whole-genome sequencing was suggested for his parents this time. The blood sample of his parents and himself was obtained with informed consent. Encouragingly, a mutation c.654C>A (p.C218X) in CD40L gene was identified, which has been reported in previous 2 studies,[6,10] whereas his mother was heterozygous and his father was wild type (Fig. 2). The mutation c.654C>A (p.C218X) could result in premature termination of CD40L synthesis. Based on the sequence analysis and elimination of the possibility of hyperimmunoglobulin M secondary to congenital rubella syndrome, the use of phenytoin, T cell leukemia, or lymphomas, the diagnosis of XHIGM was ultimately confirmed genetically up to 2 years later since the symptom onset at the young age of 16 months. Thereafter, oral administration of sulfadiazine (20 mg/kg/day bid for 10 days) and azithromycin (10 mg/kg/day qd for 10 days), intravenous immunoglobulin (IVIG, 1 g/kg once per month), and subcutaneous injection of G-CSF were immediately initiated, and the hematopoietic cell transplantation (HCT) was suggested. Regrettably, the patient abandoned the treatment because of economic factor and died 3 months after discharge.

Figure 1. Brain magnetic resonance imaging scans showing multiple nodules associating with ring-enhancing lesion in bilateral cerebral hemisphere cortex, bilateral basal ganglia, dorsal thalamus. The white matter near left side of deep island lobe, temporal lobe, and frontal lobe shows demyelination lesions (red Arrow).
3. Discussion

The XHIGM is an uncommon primary immunodeficiency disease caused by mutations in the gene for CD40L, which affects approximately 2,000,000 males and accounts for 65%–70% of all forms HIGM.[11] The importance of CD40-CD40L interaction for the biology of B cells (proliferation of B cells, Ig synthesis, isotype switch, and germinal center formation) is well established.[11] More recent data indicate that CD40L is also central to the maturation of antigen-presenting cells, in stimulating effector functions of macrophages, and in antigen priming of T lymphocytes. Therefore, those patients with XHIGM not only exhibit impaired humoral immunity, but also suffer from infections associated with defects in T cell-mediated immunity. Pneumonia is the most common infection, followed by sinusitis, recurrent otitis, and recurrent/protracted diarrhea, which is consistent with the conditions for our patient during his previous 2 disease courses. However, CNS infections, particularly for CNS toxoplasmosis, are extremely rare in patients with XHIGM. As shown in Table 3, just 3 cases of cerebral toxoplasmosis in children were reported until now.[5,12,13] According to our knowledge, this is the first case with XHIGM complicated with toxoplasmic encephalitis reported in Chinese population and it highlights the importance of CD40-CD40L interaction in cell-mediated immunity against T gondii. The susceptibility of patients with XHIGM to toxoplasmosis is probably multifactorial. Peripheral blood mononuclear cells from patients with XHIGM are identified to defect in interleukin-12 and interferon-γ production in response to T gondii that is reverted when these cells are incubated with recombinant CD40.[14] Additionally, T cells from a XHIGM patient with a previous history of toxoplasmic encephalitis lacked evidence of priming against the pathogen in vivo. These findings are consistent with the central role of the CD40-CD40L pathway for T cell priming. Finally, the toxoplasmacidal activity acquired by macrophages stimulated through CD40 together with the evidence that such a response is accompanied by in vivo restriction of parasite proliferation, which suggested that impaired macrophage effector functions may also contribute to susceptibility to toxoplasmosis in these patients.

Overall, the prognosis of patients with XHIGM is still guarded, with an average of 20% survival by age 25 years.[4] In 2016, Mt et al.[3] reported a retrospective analysis of 176 patients with XHIGM that the median survival post diagnosis was 25 years.

### Table 2

| Age, mo | IgM, g/L | IgG, g/L | IgA, g/L | IgE, IU/mL | C3, g/L | C4, g/L | CD3 (%) | CD4 (%) | CD8 (%) | CD19 (%) | NK (%) | CD4/CD8 | NEUT (×10⁶ cells/L) | LYMPH (×10⁶ cells/L) |
|---------|----------|----------|----------|------------|---------|---------|---------|---------|---------|---------|--------|---------|-----------------|--------------------|
| 1st     | 16       | 3.84     | 9.53     | 0.51       | <5      | 1.42    | 0.08    | 89.5    | 53      | 38.3    | —      | 2.4    | 1.4            | 0.05               |
| 2nd     | 23       | 2.32     | <0.33    | 0.36       | <5      | 0.84    | 0.04    | 74.7    | 38      | 34.5    | 22.3   | 0.4   | 1.1            | 0.03               |
| 3rd     | 34       | 1.78     | 1.05     | 1.24       | <5      | 0.86    | 0.10    | 85.5    | 29.6    | 50.7    | 10.2   | 2.2   | 0.6            | 0.16               |

Reference value: NEUT: 0.72–4.8 × 10⁹ cells/L, LYMPH: 1.44–7.98 × 10⁹ cells/L, CD3: 39%–73%, CD4: 25%–50%, CD8: 11%–32%, CD19: 17%–41%, CD4/CD8: 1.5–2.0, NK: 3%–16%, IgG: 3.41–19.6 g/L, IgA: 0.19–2.2 g/L, IgM: 0.43–1.83 g/L, IgE: <165 IU/mL, C3: 0.70–2.06 g/L, C4: 0.11–0.81 g/L.

![Figure 2](image.png)

Figure 2. The results of genetic sequencing that indicate the mutation of CD40L c.654C>A (exon 5), whereas his mother was a carrier and his father was wild type.
| Author          | Onset age, y | T. gondii infection | Clinical manifestations | Immunoglobulin level, g/L | The approach to diagnosis of TE | Brain MRI imaging findings | CD40L gene | Treatment                      | Prognosis |
|-----------------|--------------|---------------------|------------------------|---------------------------|-------------------------------|---------------------------|------------|--------------------------------|-----------|
| This report     | 1.4          | 2.8                 | Diarrhea, lethargy, fever, and hypologia | IgM 1.78 IgG 1.05 IgA 1.24 IgE <5 (+) | Clinical symptoms and positive PCR amplification of T. gondii in the CSF | Multiple nodules associating with ring-enhancing lesion in bilateral cerebral hemisphere cortex, bilateral basal ganglia, dorsal thalamus | C218X     | IVIG, Sulfadiazine, azithromycin, G-CSF | Died      |
| Leiva et al[12] | 2            | 10                  | Recurrent otitis media, sinusitis | IgM 7.45 IgG 6.50 IgA 1.23 IgE <0.085 (+) | Brain biopsy | Multiple enhancing nodules throughout the brain | N/D       | Pyrimethamine, Sulfadiazine, IVIG, Dexamethasone | Live      |
| Tsuge et al[5]  | 0.4          | 9                   | P. carinii/pneumonia | IgM 3.66 IgG 5.13 IgA <7.8 IgE N/D | Brain biopsy | The presence of new lesions in the cerebellum and pons | V237E     | IVIG, Dexamethasone, acyclovir, interferon α | Died      |
| Yong et al[3,8] | 41           | 41                  | Recurrent impetigo and chest infections | IgM 2.58 IgG 2.75 IgA 0.57 IgE N/D | Brain biopsy | A right thalamic mass lesion with patchy enhancement and considerable perilesional oedema | R11X      | IVIG, Sulfadiazine (a side effect of Stevens-Johnson reaction), pyrimethamine, clarithromycin | Live      |

CSF = cerebrospinal Fluid, IVIG = intravenous immunoglobulin, N/D = not mentioned, P. carinii = Pneumocystis carinii, T. gondii = Toxoplasma gondii, TE = toxoplasmic encephalitis, XHIGM = X-linked hyper-immunoglobulin M syndrome.
However, several case series in different population have demonstrated that earlier diagnosis for this disorder and the availability of more effective therapies including regular replacement treatment of IVIG and conventional antibiotics to control infection, avoidance of transfusion-related infections with hepatitis B and C to lower the prevalence of hepatitis and cirrhosis, effective therapy with natazoamide to avoid cryptosporidiosis, and the development of sclerosing cholangitis/tumors of the hepatobiliary tree could offer a hope to improve outcomes and lower mortality rates. Similarly, the HCT, as the only curative option for XHIGM currently, has been proved to improve the outcomes of those patients. Nevertheless, the transplant survival was significantly influenced by year of diagnosis and age at transplantation because persistent infections and severe organ damage were frequently observed in older patients, even before 5 years or younger.[31] Recently, an international retrospective analysis of patients with XHIGM collected from Europe, North and South America, Middle East, and Australia concluded that although the median survival time was similar for patients treated with or without HCT, those patients treated with HCT had better scores that measured general well-being and activities of daily life, and early age at diagnosis/transplantation was associated with best survival.[31]

Moreover, a recent study has proved the feasibility of engineered nuclease-directed gene repair to restore endogenously regulated CD40L, and the potential for its use in T-cell therapy for XHIGM syndrome.[15]

These aforementioned findings strongly strengthened the significance and importance of earlier and accurate diagnosis for XHIGM, yet it was difficult. The median age at diagnosis was 3.17 years (range, 1.5–7.75 years), with a median diagnostic delay of 2.84 years (range, 0.67–7.42 years). Moreover, a positive family history did not also contribute as prominently to the diagnosis as might have been expected. A study involving 28 children who born into a family, in which there was a previously affected member, showed that only 9, or study involving 28 children who born into a family, in which there was a previously affected member, showed that only 9, or

4. Conclusions

XHIGM is a rare combined immune deficiency. A delay to diagnosis is substantial because of the low awareness and recognition of the condition, which remains challenging to overcome in the future, particularly in developing countries. A timely and accurate diagnosis is imperative affecting its prognosis. A more thorough clinical history and some features such as recurrent respiratory infections, protracted diarrhea, and persistent or intermittent neutropenia accompanied with oral ulcer could increase clinical suspicion. Decreased CD4/CD8 ratio might be associated with severe clinical symptoms and a poor prognosis. Cerebral toxoplasmosis is rare in patients with XHIGM, but still should be considered. The present study firstly reported a delayed diagnosed case of XHIGM with CD40L gene c.654C>A (p.C218X) mutation complicated with toxoplasma encephalitis in Chinese population, which highlighted the importance of CD40-CD40L interaction in cell-mediated immunity against T gondii.

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