TWO BROTHERS IN A MALAYSIAN FAMILY WITH X-LINKED LYMPHOPROLIFERATIVE DISEASE - A CASE REPORT

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ABSTRACT

We report the occurrence of X-linked lymphoproliferative disease (XLP) in two brothers in a Malaysian family. In this disorder, a primary Epstein-Barr virus (EBV) infection is followed by an abnormal proliferation of transformed B-cells that cannot be controlled by suppressor T-cells, leading to the development of deranged immune function. This results in fatal infectious mononucleosis, acquired hypogammaglobulinaemia, virus-infected haemophagocytic syndrome and non-Hodgkin's lymphoma. The diagnosis should be considered when there is a family history of any male having a fulminant course of infectious mononucleosis, an otherwise benign disease. Early diagnosis is important as bone marrow transplantation is the only curative option in this disorder.

Keywords: *X-linked lymphoproliferative disease, Duncan's disease, infectious mononucleosis*

SINGAPORE MED J 1996; Vol 37: 325-327

INTRODUCTION

X-linked lymphoproliferative disease (XLP) was first described by Purtilo in 1975 after observing that 6 out of 18 males in the Duncan kindred had died of a lymphoproliferative disorder[1]. In this condition, a primary Epstein-Barr virus infection is followed by an abnormal proliferation of transformed B-cells that cannot be controlled by suppressor T-cells, leading to the development of deranged immune function. Mortality arises secondary to fulminant infectious mononucleosis, hypogammaglobulinaemia or malignant lymphoma.

Since the XLP Registry was established in 1978, more than 300 cases have been reported worldwide. To our knowledge, XLP has not been reported in Malaysia. We report the occurrence of this highly lethal condition in two brothers in a Malaysian family. We hope to increase awareness among paediatricians regarding this disease so that an early diagnosis can be made with the view to bone marrow transplantation (BMT), its only curative option.

CASE REPORT

A 2-year-old boy, previously well, was first admitted to University Hospital Kuala Lumpur (UHKL) with a 2-day history of fever and seizures. His parents were non-consanguinous and he was the younger of two male siblings in the family. He was fully-immunised and thriving. There was no significant past medical or family history. Clinically, he was mildly jaundiced with generalised lymphadenopathy. The liver was palpable 4 cm and the spleen 3 cm below their respective costal margins.

Laboratory investigations revealed a white blood count of 12.7 x 10^9/L, haemoglobin of 96g/L and platelet count of 290 x 10^9/L. Differential leukocyte count showed 63% lymphocytes (5% atypical lymphocytes), 29% neutrophils and 2% monocytes. No blasts were noted.

Examination of the cerebrospinal fluid showed 24 lymphocytes/μL, 5 polymorphs and 2 red cells/μL, proteins 86 g/dL and glucose level 4.3 mmol/L. No organism was seen on gram-stain or Indian ink smear and none was grown on culture. Bone marrow aspiration revealed hypercellular fragments with normal maturation of all 3 cell lines. No abnormal cells or excessive blasts were seen. There was no evidence of haemophagocytosis.

Immunoglobulin levels were IgG 493 mg/dL (normal), IgA 327 mg/dL (high), and IgM 1370 mg/dL (high). The IgM antibody to EBV viral capsid antigen was positive (>1:64). He was diagnosed to have EBV meningoencephalitis, treated symptomatically and discharged with residual left hemiparesis on the 29th day of hospitalisation. Following discharge, the patient defaulted follow-up and was only seen again when he was referred to UHKL from another hospital five years later.

On the third day of hospitalisation, his elder brother, aged 5 years, was admitted with a 3-day history of fever, sore throat and generalised macular-papular rash. He had mild jaundice and the liver was palpable 2 cm below the costal margin while the spleen was palpable 3cm. There was no marked lymphadenopathy.

Complete blood count revealed haemoglobin 100g/L, leukocyte count 9.3 x 10^9/L (75% lymphocytes, 8% atypical lymphocytes, 8% polymorphs, 9% monocytes) and 144 x 10^9/L platelets. The diagnosis of infectious mononucleosis was confirmed by a positive IgM antibody to EBV viral capsid antigen (> 1:32). HIV testing was not done.

Disease activity in the elder brother progressed with increasing size of liver, spleen and lymph nodes. Liver function tests were as follows: bilirubin 65μmol/L, ALP 350 U/L, AST 212 U/L, ALT 346 U/L, total protein 46 g/L and albumin 22 g/L. The prothrombin ratio was 2.5 and partial thromboplastin time was 58 seconds (control 36s). He developed pancytopaenia (Hb 62 g/L, total white blood count 2.7 x 10^9/L and platelet count 34 x 10^9/L). A bone marrow examination was not done as the child's clinical state was unstable. Immunological tests were also not done. At that point in time, the diagnosis of XLP was not considered, partly due to the extreme rarity of the disease.

Despite supportive measures, his condition deteriorated and he died 24 days after admission secondary to fulminant hepatic failure and disseminated intravascular coagulation.

At the age of 7 years, after 5 years of apparent well-being,

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the younger brother presented to a private hospital with a 3-week history of weight loss, recurrent bouts of vomiting and progressive abdominal distension.

A diagnosis of subacute intestinal obstruction was made and at laparotomy, a large tumour in the terminal ileum with omental secondaries was found. Histopathology of the tumour reported complete loss of nodal architecture with diffuse infiltration by a monomorphic population of malignant lymphoid cells. Mitotic activity was brisk. Immunostaining showed the neoplastic cells were of B-phenotype.

He was then transferred to UHKL for further management. On admission, he was cachectic and pale with evidence of bronchopneumonia and a left pleural effusion. He had ascites but no hepatosplenomegaly. Mild residual left hemiparesis remained. Results of the blood count were Hb 78 g/L, platelet count 144 x 10^9/L and white cell count 9.3 x 10^9/L (58% lymphocytes, 40% polymorphs, 2% monocytes). Bone marrow and spinal fluid examinations were normal. Cytogenetic analysis was normal (46, XY). Assay of immunoglobulin levels revealed IgG 216 mg/dL (low), IgM 40mg/dL (low) and IgA 175 mg/dL (normal). HIV testing was not done.

The diagnosis of XLP was considered then, in view of the past history and present clinical status. However, molecular genetic mapping studies to prove genetic linkage to the XLP locus were not available in the country.

Treatment for the malignant lymphoma consisted of prednisolone and high-dose cyclophosphamide, followed by dexamethasone, methotrexate, vincristine, ifosfamide, tenoposide and cytosine arabinoside. Partial parenteral nutrition was also given.

He developed severe febrile neutropaenia with septicaemic shock. Despite the use of various broad spectrum antibiotics and amphotericin B, he died on the 17th day of hospitalisation. Blood culture results which were only available post-mortem, revealed growth of multi-resistant *Flavobacterium meningosepticum*.

DISCUSSION

XLP is a sex-linked immunodeficiency disease in which the patient is selectively unable to overcome an EBV infection. The mutation on the X-chromosome predisposes affected males to an uncontrolled proliferation of abnormal B-lymphocytes following an EBV infection. This is accompanied by various other immune derangements including hypogammaglobulinaemia, T-cell and NK-cell dysfunctions which ultimately result in death from malignant lymphoma or severe infections secondary to hypogammaglobulinaemia or bone marrow aplasia. Extensive hepatocellular, myeloid and erythroid destruction also occur, secondary to an uncontrolled cytolytic T-cell response as well as the release of mediators ie interleukin-1, interleukin-2, tumour necrosis factor, alpha and gamma globulin interferon[2].

The diagnosis of XLP requires a high index of suspicion. It can be made if two or more maternally-related males manifest fatal infectious mononucleosis (IM), its complications of hypogammaglobulinaemia, malignant lymphoma or marrow hypoplasia (Table I)[3]. The two brothers in this report fulfilled the diagnostic criteria of XLP – both had fulminant IM at about the same time. The elder boy died soon after the primary infection while his younger brother died five years later of EBV-associated abdominal non-Hodgkin's lymphoma.

Abnormal T-cell, B-cell and NK-cell functions may be demonstrated with a lowered CD4: CD8 ratio in spite of their normal numbers. Other findings include a reactivation pattern of EBV serology, namely high viral capsid and early (EA) antigens and a low Epstein-Barr nuclear antigen (EBNA) titres.

In 1987, Skare, Milunsky *et al* showed that the mutation responsible was located at Xq 24-27 and this was genetically linked to a restriction fragment length polymorphism (RFLP) detected with the DXS 42 probe[4]. Prenatal detection of presymptomatic (EBV seronegative) males and carrier females is now available with RFLP analysis.

Table I – Diagnostic criteria for X-linked lymphoproliferative disease (XLP)

Diagnosis of XLP	Criteria
Definitive diagnosis of XLP	Two or more maternally-related males manifest an XLP phenotype following EBV infection
Probable diagnosis of XLP	
Major criteria	– Strong genetic linkage to the XLP locus – XLP phenotype after EBV infection
Minor criteria	Hyper IgA or IgM before EBV infection Hypo IgG 1 or IgG 3 before EBV infection Inadequate anti-EBV nuclear antigen immuno-globulin response after EBV infection Failure to undergo IgM to IgG switch following secondary challenge with 0X174
Possible diagnosis of XLP	Any male maternally-related to a male manifesting XLP phenotype

Diagnosis requires presence of at least one major and one minor criteria.

Immunoglobulin G subclass deficiency was found to be common in affected individuals before as well as after an EBV infection and this may be useful in detecting possible affected individuals especially when RFLP analysis is inconclusive or uninformative.

In the treatment of XLP, the use of immunosuppressive drugs, interferon or anti-viral agents has largely been unsuccessful, although they may control the proliferation of abnormal B-cells following an EBV infection and may eradicate activated alloreactive cytotoxic T-lymphocytes. Etoposide (VP 16) has been reported to successfully induce a clinical remission in a boy with XLP and acute infectious mononucleosis[5].

Patients with XLP are possibly more sensitive to cytotoxic drugs because a higher incidence of infectious complications has been reported[6]. Dosage reductions would be required when giving chemo-therapy for malignant lymphoma.

Bone marrow transplantation (BMT) is the only curative option as the primary abnormality is in marrow-derived cells of the immune system. So far at least five transplants have been performed for XLP. Williams et al, in reporting a successful transplant, noted that their patient's post-BMT total IgG and IgG3 subclass levels and his T-cell and B-cell numbers and activity returned to normal[7]. Vowels et al successfully performed a stem cell transplant on a patient using cells harvested from umbilical cord blood of his unaffected newborn brother who was prenatally diagnosed via chorionic villous biopsy[8].

Untreated, 60% of males with XLP disease are dead by the age of 10 years and 100% by the age of 40 years. Fatal infectious mononucleosis occurs in half of these patients while malignant lymphoma develop in 20%.

In the presence of a positive family history of XLP, the

treatment of a subsequently affected male with infectious mononucleosis should include the administration of immunoglobulins, etoposide and the urgent identification of a histocompatible donor with the view to BMT. Genetic counselling should include, where possible, the identification of asymptomatic males by RFLP analysis.

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