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Haematological manifestations of X-linked lymphoproliferative disease

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Abstract

X-linked lymphoproliferative disease (XLP) is a rare genetic disorder that occurs predominantly in boys. There are two types of the disease, each with different clinical and genetic characteristics. XLP1 is caused by the mutation in the SH2D1A gene and XLP2 is associated with the mutation in XIAP/BIRC gene. Genetic defects lead to the dysfunction of the immune system. Additionally, Epstein-Barr virus infection plays a major role in the development of the disease. Clinical manifestation varies significantly, even among family members who carry the same mutation. The disease most often manifests with haemophagocytic lymphohistiocytosis, dysgammaglobulinemia, fulminant infectious mononucleosis, splenomegaly, and B-cell lymphomas localized near the ileocecal valve, and colitis. Differential diagnosis should primarily consider more frequent disorders with an impaired immunological response. XLP is a fatal disease, but with the development of new treatment options, patients' life expectancy has increased significantly. Currently, the only definitive treatment is an early allogeneic hematopoietic stem cell transplantation. The onset of severe symptoms before transplantation largely reduces the patient's chances of therapeutic success. As a result, it is crucial to make an early diagnosis. New therapies that include enzyme inhibition, gene therapy, and gene editing are very promising. Patients and their families should be provided with genetic counselling and the possibility of preimplantation diagnostics.

Key words: X-linked lymphoproliferative disease, X-linked recessive, immunodeficiency, hematopoietic stem cell transplantation, haemophagocytic lymphohistiocytosis

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Introduction

X-linked lymphoproliferative syndrome (XLP) is a primary immunodeficiency disorder. The incidence is estimated at 1–3 cases per million men [1, 2], however, it seems to be underestimated [3, 4]. The disease is inherited in an X-linked recessive pattern, therefore only a few cases have been reported in women [5] who probably had skewed X-chromosome inactivation. Epstein-Bárr virus (EBV) infection, in addition to the genetic predisposition, has a crucial role in the pathogenesis of XLP

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[6]. The disease was first reported in the 1970s by Purtilo et al. who described the affected members of the Duncan family, hence the interchangeable names of XLP: Duncan's disease or Purtilo's syndrome [6, 7]. The study aims to draw attention to the fortuitous and often delayed diagnosis, which results from rare incidences and a diversity of clinical signs and symptoms.

Pathogenesis

Two types of the X-linked lymphoproliferative syndrome have been classified: XLP1 caused by a mutation in the *SH2D1A* gene and XLP2 caused by a mutation in the *XIAP/BIRC* gene [2, 8]. Both genes are at position Xq25 [9]. Due to the genetic and clinical differences in the types of the disease, this study describes the more common XLP1 [8]. The link between the mutation in the *SH2D1A* gene and XLP1 was identified in 1998 [8]. Since then, more than 140 different types of mutations have been described (http://www.hgmd.cf.ac.uk/ac//gene.php?gene=SH2D1A).

The *SH2D1A* mutation leads to the functional and developmental defects of T, NK, iNKT cells and indirectly of B lymphocytes [2, 10]. The *SH2D1A* gene encodes the cytoplasmic protein SAP (*SLAM-associated protein*) necessary for the proper functioning of the immune system. This protein participates in the regulation of signal transduction pathways through SLAM receptors (signalling lymphocytic activation molecules) [9]. SAP is critical for the proper development of iNKT cells, T CD8+ and NK cells cytotoxicity. Lack of SAP function leads to disruption of the cell's apoptosis process and excessive activation of diacylglycerol alpha kinase (DGKα). The inhibition of DGKα has become the subject of research on therapy for XLP [11, 12]. T lymphocytes play an important role in the formation of germinal centres. These structures contain memory B cells and plasma cells, consequently switching of immunoglobulin classes occurs there. In patients with XLP, the formation of germinal centres is inhibited due to dysfunctional T cells, which results in the abnormal production of antibodies [7, 13].

Ebstein-Bárr virus contributes significantly to the pathogenesis of XLP. Majority of genetically predisposed individuals present with clinical symptoms of the disease after EBV infection occurs. However, approximately 10–12% of patients have disease manifestations before exposure to the virus [2, 6, 9].

PCR is the most relevant diagnostic tool for EBV infection among patients with XLP [6].

Symptoms

The lack of correlation between genotype and phenotype makes it difficult to predict the course of the disease in a given patient [2, 13]. Even among members of the same family who share the same mutation, the clinical picture may differ significantly [2, 6].

Usually, the first symptoms appear in early childhood between the ages of 2 and 5 [2, 14]. The average survival time of patients who did not undergo allogeneic hematopoietic stem cell transplantation allo-HSCT is 11 years [14]. Only half of the patients survived into adulthood according to a study by Schmid et al. [13].

The clinical manifestation of XLP1 is very variable. The condition may present as life-threatening fulminant infectious mononucleosis (FIM), haemophagocytic lymphohistiocytosis (HLH), malignant non-Hodgkin lymphoma, or Hodgkin lymphoma. Other patients develop dysgammaglobulinemia accompanied by recurrent infections [2, 15]. Less commonly aplastic anaemia, vasculitis, or chronic gastritis have been reported [2, 8]. It should be emphasized that some authors consider FIM and HLH as a single clinical manifestation [13].

According to available sources, there are various reports regarding the most common clinical manifestation of XLP1. Several authors suggest HLH [5, 7], which presents with fever and hepatosplenomegaly and leads to death in over half of the patients [7]. The diagnostic criteria of HLH are included in Table 1 [16].

Patients with XLP infected with EBV should be carefully monitored for the development of haemophagocytic lymphohistiocytosis, as it is

Table 1. Criteria for the diagnosis of haemophagocytic lymphohistiocytosis [16]

For the diagnosis, it is necessary to fulfil ≥ 5 criteria:
1) fever ≥ 38.5°C
2) splenomegaly
3) peripheral blood cytopenias ≥ 2 out of 3 lines (haemoglobin < 9 g/dL, platelets < 100,000/μL, neutrophils < 1,000/μL)
4) hypertriglyceridemia [fasting ≥ 3 mmol/L (265 mg/dL)] and/or hypofibrinogenemia (< 150 mg/L)
5) hyperferritinemia ≥ 500 μg/L
6) haemophagocytes in bone marrow, CSF or lymph nodes
7) decreased or no NK cell activity
8) sCD25 (soluble interleukin 2 receptor) concentration ≥ 2400 U/mL

CSF — cerebrospinal fluid; NK — natural killer

more common in this group than in EBV-negative patients [6, 13].

About half of patients with XLP present with an impaired humoral response. An incompetent immune system may lead to recurrent infections or ineffective vaccinations, but the patient may also remain asymptomatic [7]. A case report was found describing a boy infected with measles after measles vaccination. In addition, the boy did not develop antibodies against hepatitis B after vaccination [8]. In laboratory findings, dysgammaglobulinemia may range from agammaglobulinemia to polyclonal hypergammaglobulinemia [15].

Fulminant infectious mononucleosis results from abnormal T cell response to EBV infection [17]. Lymphadenopathy, hepatosplenomegaly, and bone marrow failure may appear in the course of the disease. Recent reports suggest that the incidence of the disease has decreased from 60–75% to 30–40% in patients with XLP [9]. Over the past years, the mortality of FIM has decreased from over 90% to about 65% [9]. The major cause of death in these patients is hepatic failure [6].

Another common manifestation of XLP1 is hematopoietic malignancy. The incidence, according to various authors, ranges from 19.6% [7] to 30% [13]. The lack of iNKT cells leads to the absence of peripheral immunosurveillance against tumours [18]. The most commonly described neoplasm is non-Hodgkin B-cell lymphoma in the ileocecal region [6, 19]. A higher risk of neoplasms should draw the attention of the physician to the occurrence of non-specific symptoms: fatigue, fever, lymphadenopathy, weight loss, and night sweats.

There is a noticeable relationship between EBV infection and the frequency of the particular symptoms. In the majority of patients with HLH, EBV infection was the trigger for its development [13]. Dysgammaglobulinemia occurs more frequently in EBV-negative patients [6, 7]. More detailed data are presented in Table 2. Booth et al. [2] reported no statistically significant differences in mortality between EBV-positive and EBV-negative patients.

It should be emphasized that symptoms of the less common form of XLP (XLP2) may differ from those described above. In XLP2 the most common manifestations are splenomegaly [13], haemophagocytic lymphohistiocytosis, inflammatory bowel disease, and, less frequently, dysgammaglobulinemia, fever, arthritis, erythema nodosum [20]. Compared to XLP1, XLP2 is not related to an increased risk of malignancy [13]. HLH is more common in the course of XLP2 and may recur [13]. Table 3 presents the main differences in the frequency of particular phenotypes in patients with XLP1 and XLP2.

Table 2. The relationship between the presence of Epstein-Bárr virus (EBV) infection and the frequency of particular clinical manifestations of X-linked lymphoproliferative syndrome (XLP) 1 [7]

Manifestation	EBV-positive patients [%]	EBV-negative patients [%]
Dysgammaglobulinemia	37.2	51.8
Lymphomas	19.6	25.0
Haemophagocytic lymphohistiocytosis (HLH)	51.0	21.4

Table 3. Comparison of the frequency of disease phenotypes between X-linked lymphoproliferative syndrome **(XLP) 1** and XLP2 (based on [6, 7, 13, 20])

Disease	XLP1	XLP2
Haemophagocytic lymphohistiocytosis (HLH)	51–55%	76%
Dysgammaglobulinemia	50–67%	33%
Splenomegaly	7%	57–87%
Lymphomas	25–30%	Population risk

Differential diagnosis

XLP should be considered in a patient with a severe or atypical course of EBV infection. Particularly if the patient is a male infected in the first decade of life and similar cases have been reported in his family. Currently, a significant percentage of patients are diagnosed based on genetic tests performed due to other affected individuals described in family history [3, 7].

Moreover, extra-nodal Burkitt's lymphomas located in the ileocecal region should make the clinician think of XLP [6, 19]. A distinct lymphoma that develops de novo in a young boy who underwent chemotherapy for primary lymphoma should raise clinical awareness as well [6].

Common variable immunodeficiency (CVID) is a primary immunodeficiency disorder with a much higher incidence than that of XLP (about 1 in 30,000). CVID usually manifests itself in the second decade of life in both women and men. The disease is characterized by increased susceptibility to infections, most often in the upper respiratory tract, and by hypogammaglobulinemia in laboratory tests [6, 21].

XLP should be also differentiated from familial haemophagocytic lymphohistiocytosis (FHL). The disease is inherited in an autosomal recessive manner and affects both genders. The mutation leads to overproduction and excessive activation of immune system cells, and as a result development of HLH. Its course does not differ clinically from HLH in patients with the *SH1D2A* gene mutation [6].

Mutations leading to the development of XLA (X-linked agammaglobulinemia) [15] and XMEN (X-linked immunodeficiency with magnesium defect, EBV infection, and neoplasia) [22], similarly to XLP, are inherited in an X-linked recessive manner. Both should be considered in young male patients presenting with immune disorders.

Disorders inherited in an autosomal manner occur in both sexes with the same prevalence. Two examples that should be differentiated with XLP are ITK deficiency (interleukin-2-inducible T-cell kinase deficiency) [6, 23] and CD27 deficiency [6]. The diseases are clinically indistinguishable. The only way to distinguish these three diseases is through genetic testing.

Chediak-Higashi syndrome is a defect of the immune system that manifests itself in the form of recurrent severe infections, splenomegaly, and fever. The presence of partial albinism, photosensitivity, and peripheral neuropathy distinguishes it from XLP [6].

Treatment

To date no therapy has been found to cure all the patients, thus XLP is still considered a fatal disease. Originally the treatment included acyclovir, IFN-gamma and alpha, cyclosporin A, and intravenous immunoglobulins (IVIG) which is still used [8, 24]. Due to the change in therapeutic protocols, overall mortality in patients with XLP1 has decreased from 75% to 29% [7].

Flow cytometry may be used at the beginning of the diagnostic process to measure the expression of SAP protein or study lymphocyte populations [25]. After confirming the diagnosis with gene sequencing, it is essential to take a thorough patient's history, perform a physical examination, and order laboratory and imaging tests. During the physical examination, features that may indicate infections and more severe manifestations of the disease should be noted. In laboratory tests, particular attention should be paid to abnormal blood counts, clotting times, acute-phase protein levels, liver transaminases, bilirubin, TAG, and lactate dehydrogenase (LDH). Additionally, bone marrow biopsy and cerebrospinal fluid testing are recommended [6].

Currently, allo-HSCT is the only method that allows the patient to be cured. HSCT should be considered as soon as possible in all individuals, taking into account the severity of the disease and the general condition of the patient [2, 7, 8]. Convincing an asymptomatic patient or his family to undergo stem cell transplantation may be very challenging. The physician must be properly prepared to present the benefits and risks associated with HSCT [7]. Most patients tolerate the procedure well and their immune system regains its function. Reactivation of EBV infection and post-transplant lymphoproliferative disease are possible and rare complications [2]. Fear of them should not delay the decision about the transplant [6]. The survival rate after HSCT reaches 81.4% and decreases below 20% without the transplant [2, 7]. Preparation for transplantation involves treating the already developed symptoms of the disease and stabilizing the patient's condition [26]. Whenever possible EBV-positive donors are recommended for EBV-positive recipients [7]. It seems to be advantageous for asymptomatic individuals with hypogammaglobulinemia to administer immunoglobulin replacement therapy intravenously (IVIG) every 3–4 weeks or subcutaneously once a week [7]. Nonetheless, it should be acknowledged that long-term administration of antibodies is associated with consequences in the structure and function of B cells. Consequently, IVIG use should be restricted for patients awaiting transplantation [27].

Treatment of lymphohistiocytic haemophagocytosis, one of the most common manifestations of XLP, remains a challenge, nevertheless, new treatment strategies have significantly improved survival. Keeping in mind that HLH develops more often in EBV-positive patients administration of Rituximab immediately after EBV infection is considered [24]. Rituximab is an anti-CD20 monoclonal antibody that reduces the population of B cells hosting the virus. Therapy has been proven to be effective but carries the risk of hypogammaglobulinemia [7]. If a patient develops HLH, therapy with steroids, etoposide, and cyclosporine should be initiated [6, 7]. In the case of neurological symptoms, methotrexate and intrathecal steroids are added [7]. Currently, the research on HLH treatment with the use of tocilizumab (anti-IL6R antibody), anti-IFN-gamma monoclonal antibodies, and ruxolitinib (JAK1/2 kinase inhibitor) is in progress [7].

The remaining manifestations of XLP are treated according to standard protocols, regardless of the SH2D1A mutation [26].

It is assumed that inhibition of diacylglycerol kinase alpha (DGKα) will suppress the expansion of T cells and restore their sensitivity to apoptosis. Blocking of DGKα in mice with a defect in SAP and EBV infection has led to satisfactory results [11, 12].

Gene therapy is another promising solution in the treatment of XLP1. Studies performed on mice with the use of autologous *SH2D1A* gene transfer resulted in significant improvement in the functioning of the immune system in these animals. The effectiveness of this therapy does not differ from HSCT [10], furthermore, it is associated with reduced toxicity, a lower amount of chemotherapeutic agents used by the patient, and no risk of graft versus host disease. Unfortunately as a result of the integration of gammaretroviral material near the proto-oncogenes the first few attempts of gene therapy led to the development of leukaemias and myelodysplasia [6, 7].

Gene-editing therapy is currently developing. It involves removing and replacing damaged genetic material with the correct copies of DNA. In patients with disorders caused by a single mutation, this seems to be an effective method. However, this form of therapy may not be useful in the case of the deletion of the SAP gene. Moreover, gene editing has to be adjusted individually for each patient, which is time-consuming and associated with high costs [7]. Along with evolving technology, it may be worth considering placing genetic material in a DNA bank. Future research may enable and emphasize the efficacy of personalized therapy [6].

Women who are aware of being carriers of the mutation in the *SH2D1A* gene should consider the possibility of preimplantation diagnostics when planning a pregnancy because the risk of passing the defective gene is 50% with each pregnancy. This requires undergoing in vitro procedure but eliminates the risk of disease in offspring [28]. To exclude the disease in a developing foetus, chorionic villus sampling and amniocentesis may be performed [6].

The uncertain prognosis of the disease and the possibility of passing the defective gene to the offspring may harm the mental health of patients. It is necessary to provide psychological support and bear in mind that patients' families may also need it.

Summary

Essential concepts for every paediatrician to keep in mind:

- thoroughly obtain family history, especially in terms of immunodeficiency symptoms.
- think about immunodeficiency in families with unexplained deaths of infants.
- ineffective vaccinations may be the first sign of XLP.
- consider XLP in young males with HLH, severe or atypical course of infectious mononucleosis, and B-cell lymphoma localized in the ileocecal region.

Conflict of interest

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Ethic

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