X-Linked Lymphoproliferative Disease (XLP)

By
Ali Sobh, MD
Lecturer of Pediatrics
Mansoura Faculty of Medicine, Egypt
ASID Newsletter 2017
X-Linked Lymphoproliferative Disease
XLP, also called Duncan disease, is a rare disorder first described in 1975 by Purtillo, et al in the Duncan family, in which 6 of 18 males died of lymphoproliferative disease.
Two genetic causes are responsible for XLP.

- XLP type 1 (XLP-1) is caused by hemizygous mutations in the gene *SH2D1A* encoding the signaling lymphocyte activation molecule (SLAM)–associated protein (SAP).
- XLP type 2 is caused by hemizygous mutations in the gene encoding X-Linked Inhibitor of apoptosis protein (XIAP; also termed *BIRC4*).
XLP Type 1

- It is caused by mutations in the signaling lymphocyte activation molecule (SLAM)-associated protein (SAP) gene.
- Inherited in an X-linked recessive manner.
- A worldwide XLP registry was established in 1980 as a resource for diagnosis, treatment, and research.
SH2D1A (SH2 domain protein 1A) has 4 exons and codes for a small protein, SAP, with only 128 amino acids that form 1 SH2 domain (amino acids 6-104). Previously unreported mutations observed in patients with XLP1 tested through the DCHI at Cincinnati Children’s Hospital are shown.

Alexandra et al, 2010
PATHOGENESIS

- The exact mechanisms underlying the clinical features of XLP remain unclear.
- EBV infection is particularly prominent in patients with XLP.
- SAP is expressed in T cells, NK cells, invariant natural killer T (iNKT) cells, and some B cells.
(a) Signaling pathways downstream of SLAM in T cells. In T cells, SAP and its SLAM-SAP-Fyn signaling module regulate cytokine production by activating two pathways: one is SHIP, and the other involves PKCq, Bcl10 and NF-kB.

(b) Signaling pathways downstream of 2B4 in NK and CTL cells. In NK and CTL cells, a 2B4-SAP-Fyn module triggers a pathway involving at least EAT-2 and Csk, which activates cell cytotoxicity. (c) Signaling pathways downstream of NTB-A in NK cells. In NK cells, NTB-A appears to play a similar role to the 2B4 pathway, which can bind SHP-2, but not SHP-1.

Xi Yang et al, 2012
• SAP defective T cells do not provide adequate B cell help, which may contribute to the hypogammaglobulinemia and humoral immunodeficiency seen in patients with XLP.

• A decrease in apoptosis due to deficiency of SAP may underlie the intense, unchecked CD8+ T cell cytotoxicity stimulated by acute EBV infection in patients with XLP.

• SAP normally inhibits interactions between the 2B4 receptor and negative regulatory molecules. Thus, NK cell activation is inhibited by 2B4 when SAP is absent, leading to reduced NK cell lysis of EBV-infected B cells.
The average age at presentation, usually triggered by Epstein-Barr virus (EBV) infection, is 2.5 years.

Most affected individuals have no apparent disease prior to presentation, despite their immunologic abnormalities that are present prior to EBV infection.

In a retrospective series of 91 patients with confirmed XLP, the median age of presentation was four years in patients who were EBV positive and three years in those who were EBV negative.

Booth et al, 2011
The three most common phenotypes of XLP are:

- Fulminant infectious mononucleosis (FIM) due to an abnormal immune response to EBV infection (58 percent)
- Dysgammaglobulinemia (22 to 31 percent)
- Lymphoproliferative disease, including lymphoma, usually of B cell origin (30 percent)

Sumegi et al, 2000
- Somatic reversion is a spontaneous genetic change in a disease-causing mutation at the level of a single lymphoid precursor cell that reverts the gene back to normal.
- Reverted cells that showed SAP expression and function, indicating a reversion process, were identified in 12 XLP patients from 10 different kindreds.
- Somatic reversion was found exclusively within CD8+ T cells with an effector memory phenotype.

*Palendira et al, 2012*
DIAGNOSIS

- Testing for XLP should be considered in all males diagnosed with
  - CVID or other hypogammaglobulinemia
  - HLH (especially if Epstein-Barr virus [EBV] associated);
  - Severe infectious mononucleosis
  - Lymphoma (especially B cell, non-Hodgkin lymphoma affecting extranodal sites).

- Males with a family history of known or suspected XLP

- Prenatal testing is possible for pregnancies of women who are heterozygous XLP carriers, and in vitro fertilization with preimplantation genetic diagnosis of embryos may also be available
- Flow cytometry is available as a screening tool to quickly diagnose cases of XLP in which protein is not expressed.
- Flow-cytometric SAP determination can be combined with a functional measurement of 2B4-mediated NK cell killing of EBV-infected cells when SAP expression is reduced but not absent.
- Patients are generally screened for mutations in the Src homology 2 domain protein 1A (SH2D1A), which encodes the signaling lymphocyte activation molecule (SLAM)-associated protein (SAP).
MANAGEMENT

- Antiviral agents and IVIG in the setting of acute EBV infection.
- Rituximab (anti-CD20), which has been used successfully in a few patients to control acute primary EBV infection.
- Patients treated with rituximab should be carefully monitored for hypogammaglobulinemia and receive preemptive immune globulin replacement therapy.
- HLH should be treated with HLH specific therapy to induce remission prior to hematopoietic cell transplantation (HCT).
- Lymphoma should be treated with standard chemotherapy for the specific type of lymphoma and should achieve clinical remission if possible prior to undergoing HCT.
PREVENTIVE THERAPY

- IVIG replacement therapy has been used to prevent primary infection or acute reactivation of EBV in patients with XLP.
- RITUXIMAB was shown to prevent severe EBV infection and clinical deterioration prior to allogeneic HCT in EBV-negative individuals.
- Preemptive therapy for asymptomatic affected male relatives, in particular siblings in the same household as a symptomatic case, should be considered.
CURATIVE THERAPY

- HCT is the only curative treatment for XLP
- In one large series, 43 patients underwent a total of 46 transplants between 1997 and 2009.
  - Overall survival was approximately 81 percent, with a higher rate seen if a matched family donor was used (92 percent) and if HLH was not the main clinical manifestation of XLP.
  - Survival after HCT was 50 percent in those with HLH, and all of the patients who died exhibited HLH as their main disease manifestation.
- Gene therapy is under investigation for XLP, with promising preliminary results in a murine model

Booth et al, 2011
PROGNOSIS

- In 1995, the overall survival was reported to be 25 percent,
- Survival has improved since then with the advent of better treatment options.
  - Two main factors responsible for better survival are the preemptive use of Rituximab in Epstein-Barr virus (EBV)-naïve patients and concomitant Immune globulin replacement therapy to prevent lethal EBV infection
  - HCT, such that the previous mortality of approximately 70 percent has changed to approximately 70 percent long-term survival.

  *Booth et al, 2011*
XLP type 2

- The XIAP/\textit{BIRC4} gene was initially characterized in 1996.
- However, the association with human disease was not discovered until 2006 when Rigaud \textit{et al} found that mutations of XIAP/\textit{BIRC4} were associated with XLP phenotypes in 12 patients from 3 kindreds who lacked \textit{SH2D1A} mutations.2
XIAP/BIRC4

*BIRC4* (baculoviral IAP repeat-containing protein 4) is composed of 6 exons and codes for XIAP, which is 497 amino acids long. XIAP contains 3 BIR domains and 1 RING domain. Mutations observed in patients with XLP2 tested through the DCHI at Cincinnati Children’s Hospital and by Rigaud et al, 2006 and Zhao et al, 2010 are shown.

*Alexandra et al, 2010*
PATHOGENESIS

• XIAP is a member of the inhibitor of apoptosis protein (IAP) family.

• XIAP has been implicated in a variety of pathways; however, as indicated by its name, the first function ascribed to this protein was an anti-apoptotic activity.

• XIAP inhibits programmed cell death by directly binding to and blocking activated forms of the effector caspases 3, 7 and 9.

• XIAP is involved also in NFκB activation, TGF-β receptor signaling, activation of the MAPK pathway, copper metabolism and autophagy.
Importantly, recent findings also indicated that XIAP has a direct role in innate immunity and the negative regulation of inflammation.

- XIAP is required for signal transduction and function of the nucleotide oligomerization domain receptor (NOD)-like pattern recognition receptors (NLRs) NOD 1 and 2.
- Studies in mice show that XIAP is a negative regulator of TNFR1-dependent pro-inflammatory cytokine production and NLRP3 inflammasome activation in myeloid cells.
In XIAP deficiency, innate and adaptive responses are compromised, leading to accumulation of infectious pathogens (and the associated PAMPS) and subsequent uncontrolled activation of the inflammasomes, which is not properly regulated in the absence of XIAP. In this context, there is accumulation of pro-inflammatory cytokines such as TNF-Alpha, IL-1beta and IL-18, and increased cell-death of lymphocytes, myeloid cells and possibly other cell types. This results in a high chronic inflammatory environment leading to splenomegaly, IBD and HLH.

*Latour and Aguilar, 2015*
CLINICAL PRESENTATION

- Since its original discovery, more than 70 male patients from different countries have been diagnosed with an XLP-2/XIAP deficiency.
- XIAP deficiency is mostly a pediatric disease and boys can be affected very early in their life (during the first months) with symptoms which are especially severe.
- The most frequent clinical manifestations are
  - HLH (54%) (EBV is very often the trigger of HLH in more than 60% of cases)
  - recurrent splenomegaly (57%)
  - IBD (26%).

Aguilar and Latour, 2015
## Clinical Presentation

<table>
<thead>
<tr>
<th>Country</th>
<th>Patients (n)</th>
<th>HLH (n)</th>
<th>EBV&lt;sup&gt;a&lt;/sup&gt; (n)</th>
<th>IBD (n)</th>
<th>Hypog.&lt;sup&gt;b&lt;/sup&gt; (n)</th>
<th>Splenomegaly (n)</th>
<th>Skin abscesses and other inflammatory manifestations (n)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>35</td>
<td>25</td>
<td>20</td>
<td>8</td>
<td>4</td>
<td>18</td>
<td>2</td>
<td>7, 8 and &amp;&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>England</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td>7, 8, and &amp;&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Germany</td>
<td>33</td>
<td>12</td>
<td>8</td>
<td>10</td>
<td>5</td>
<td>19</td>
<td>2</td>
<td>9, 10, 28, 29</td>
</tr>
<tr>
<td>USA</td>
<td>11</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>10</td>
<td>ND</td>
<td>11, 26</td>
</tr>
<tr>
<td>Japan</td>
<td>12</td>
<td>7</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>ND</td>
<td>9, 27</td>
</tr>
<tr>
<td>TOTAL</td>
<td>100</td>
<td>54</td>
<td>36</td>
<td>26</td>
<td>16</td>
<td>57</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> EBV as trigger of HLH or patients with severe infectious mononucleosis at onset

<sup>b</sup> Hypogammaglobulinemia

<sup>c</sup> Aguilar and Latour, unpublished observations

---

Aguilar and Latour, 2015
 DIAGNOSIS

- A diagnosis of XIAP deficiency must always be considered in boys presenting with HLH in the course of viral infection.

- XIAP deficiency must also be considered in boys with severe IBD - especially when combined with splenomegaly, HLH and/or a family history of IBD.
Diagnosis

- Detection of XIAP by flow cytometry may be used for diagnosis but this technique cannot dependably identification mutations that maintain some degree of protein expression.
- Functional assay, an easy, reliable way of screening patients has emerged by looking at intracellular TNF-α production by PBMCs in response to MDP (the ligand of NOD2), which is abolished when XIAP is defective.
- The most definitive way to diagnose XIAP deficiency is to sequence the gene itself.
MANAGEMENT

- HLH and IBD symptoms are treated with classical immunosuppressive drugs including etoposide, corticosteroids and cyclosporine for HLH and corticosteroids, azathioprine, mesalazine and anti-TNF for or IBD
- Hypersplenism can require splenectomy and several patients with IBD had colectomy
- The only curative treatment is a hematopoietic stem cell transplant.
- Nevertheless, HSCT in XIAP deficiency has been associated initially with a bad prognosis.
### XLP1 vs XLP2

<table>
<thead>
<tr>
<th></th>
<th>SAP-/Y, n (%)</th>
<th>XIAP-/Y, n (%)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLH</td>
<td>18 of 33 (55)</td>
<td>22 of 29 (76)</td>
<td>NS</td>
</tr>
<tr>
<td>HLH relapses (/HLH-survivors)</td>
<td>2 of 7 (29)</td>
<td>11 of 14 (79)</td>
<td>NS</td>
</tr>
<tr>
<td>EBV at first HLH</td>
<td>11 of 12 (92)</td>
<td>15 of 18 (83)</td>
<td>NS</td>
</tr>
<tr>
<td>Fatal HLH</td>
<td>11 of 33 (33)</td>
<td>5 of 30 (17)</td>
<td>NS</td>
</tr>
<tr>
<td>Fatal HLH (/HLH patients)</td>
<td>11 of 18 (61)</td>
<td>5 of 22 (23)</td>
<td>.0230</td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td>14 of 21 (67)</td>
<td>8 of 24 (33)</td>
<td>.0377</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>10 of 33 (30)</td>
<td>0 of 30 (0)</td>
<td>.0010</td>
</tr>
<tr>
<td>Cytopenias (in the absence of</td>
<td>4 of 33 (12)</td>
<td>11 of 21 (52)</td>
<td>.0020</td>
</tr>
<tr>
<td>full-blown HLH)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenomegaly (in the absence</td>
<td>2 of 29 (7)</td>
<td>20 of 23 (87)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>of full-blown HLH)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic colitis</td>
<td>0 of 33 (0)</td>
<td>5 of 30 (17)</td>
<td>.0203</td>
</tr>
</tbody>
</table>

Pachlopnik et al, 2011
Thank You