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Registered Charity No 1111075

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X-Linked Lymphoproliferative Syndrome

XLP-2

Registered Charity Number 1111075

Background

In 2006 a second form of XLP was identified through looking at specific gene mutations. This occurs in approximately 20% of XLP cases and is now called X-Linked Lymphoproliferative Syndrome type-2 (or XLP-2 for short) with the initial XLP being reclassified as XLP-1. XLP-2 therefore is an even rarer genetic condition than XLP-1, but the impact onto boys with the condition is no less severe.

Characteristics of XLP-2

XLP-2 is diagnosed when there is mutation in the gene *XIAP* (also known as *BIRC4),* but does not have a detectable defect in gene *SH2DIA* (the gene associated with XLP-1). In addition XLP-2 boys have a normal expression of SAP (SLAM Associated Protein) unlike XLP-1 affected boys.

Both XLP-2 (*XIAP*) and XLP-1 (*SH2DIA*) genes are located in the same gene locus (*Xq25*) and the two genes are only separated by a physical distance of 2.5 Mb.

There are a number of similarities of XLP-2 and XLP-1 and also a number of key differences.

As with XLP-1, XLP-2 infected boys have a significantly increased susceptibility to EBV infection and subsequent consequences of that infection. Both XLP-1 and XLP-2 boys are at risk of:-

- Severe infectious mononucleosis (also known as glandular fever or mono)
- Hypogammaglobulinemia (low levels of immunoglobulin)
- Hemophagocytic Lymphohistiocytosis (HLH) or virus-associated hemophagocytoc syndrome (VAHS)

Most XLP-2 affected boys develop HLH related to EBV infection but in some cases they show HLH without having EBV as the obvious trigger. Typical symptoms of HLH besides persistent fever are pallor (paleness), jaundice, liver and spleen enlargement, and neurological symptoms, such as irritability or even seizures. The involvement of the bone marrow, the site of blood cell production, can lead to severe decline of the blood cell counts (red and white blood cells and platelets).

Before encountering EBV, XLP-2 boys are healthy but unlike XLP-1 boys, some of them develop splenomegaly (an enlargement of the spleen) as the first sign of their disease which may represent minimal forms of HLH.

The key difference with XLP-1, is that XLP-2 boys do not seems to be at increased risk to develop lymphoproliferative disorders such as lymphomas. Indeed it would actually appear that the absence of *XIAP* may actually protect XLP-2 boys from cancer, more medical research is currently underway into this.

Treatment for XLP-2 Boys

This is principally the same for both XLP-2 and XLP-1 affected boys.

Initial treatment should include regular immunoglobulin treatment. This will give some level of protection against possible infections including EBV, but is not a cure. Please see the XLP Research Trust's leaflet on immunoglobulin for more information.

It is likely that the only cure for XLP-2 will be a bone marrow transplant which in effect replaces the faulty immune system with a healthy donor one; however because of the small number of cases this has not yet been confirmed.

Medical research is underway looking at possible other alternative treatments such as gene therapy but this is still some years away from being a proven solution.

Conclusions

The discovery of XLP-2 and the ability now to accurately diagnose it in a patient will be helpful to correctly and more quickly prescribe the correct treatments for affected boys.

It also possible that there could be other forms of XLP as yet undiscovered which are caused by a different faulty gene but manifesting the same problems. However if this is the case then this will affect an even smaller number of boys.