X-linked agammaglobulinaemia – XLA

Background by Dr David Webster

XLA has some historical significance in the field of immunology. It was the first recognised PID, originally described in an 8 year old boy in 1952 by a physician in the American army, Colonel Ogden Bruton. The diagnosis was made possible by a technical advance in measuring gammaglobulins/immunogobulins in the blood, which were subsequently shown to consist of antibodies that protected against a variety of infections. Bruton not only discovered the first PID but he was the first to use purified immunoglobulin as a treatment, made possible by the American army's research interest into fractionating proteins from the blood for potential use in wounded soldiers. Although rare and only affecting boys, XLA has taught us a lot about the importance of antibodies in protection against microbes, and also about how and where in the body antibodies are made. In the 1980s it became clear that most XLA patients could not make B lymphocytes in the bone marrow, these being the cells that develop into antibody producing cells. By studying the inheritance of XLA it became possible in the early 1990s to identify the genetic defect, the disease being the first PID to be understood at a molecular level.

XLA is nearly always inherited from the mother (the carrier), the defect in the relevant gene (called BTK because it codes for the protein Bruton's tyrosine kinase) being carried on one of the two maternal X-chromosomes. The mothers are healthy because the normal gene on the other X-chromosome compensates. Because males only have one X-chromosome, inheriting the affected chromosome causes the disease. On average, half the boys of a 'carrier' mother will have XLA, and half the daughters will be healthy 'carriers' (see diagram). However, like tossing a coin, luck can be against you and I know of families where the first two or three boys were all affected. By looking at the mother's pedigree and childhood deaths from infection in boys before the 1960s, you can sometimes trace the defect back to where it probably started as a spontaneous mutation in the BTK gene. Such mutations still occur and explain the occurrence of a first boy with XLA in a family. Although affected men can pass the defective gene to some of their children, the good news is that none of their sons will have XLA, although all their daughters will be healthy carriers and could pass the disease on to the next generation.

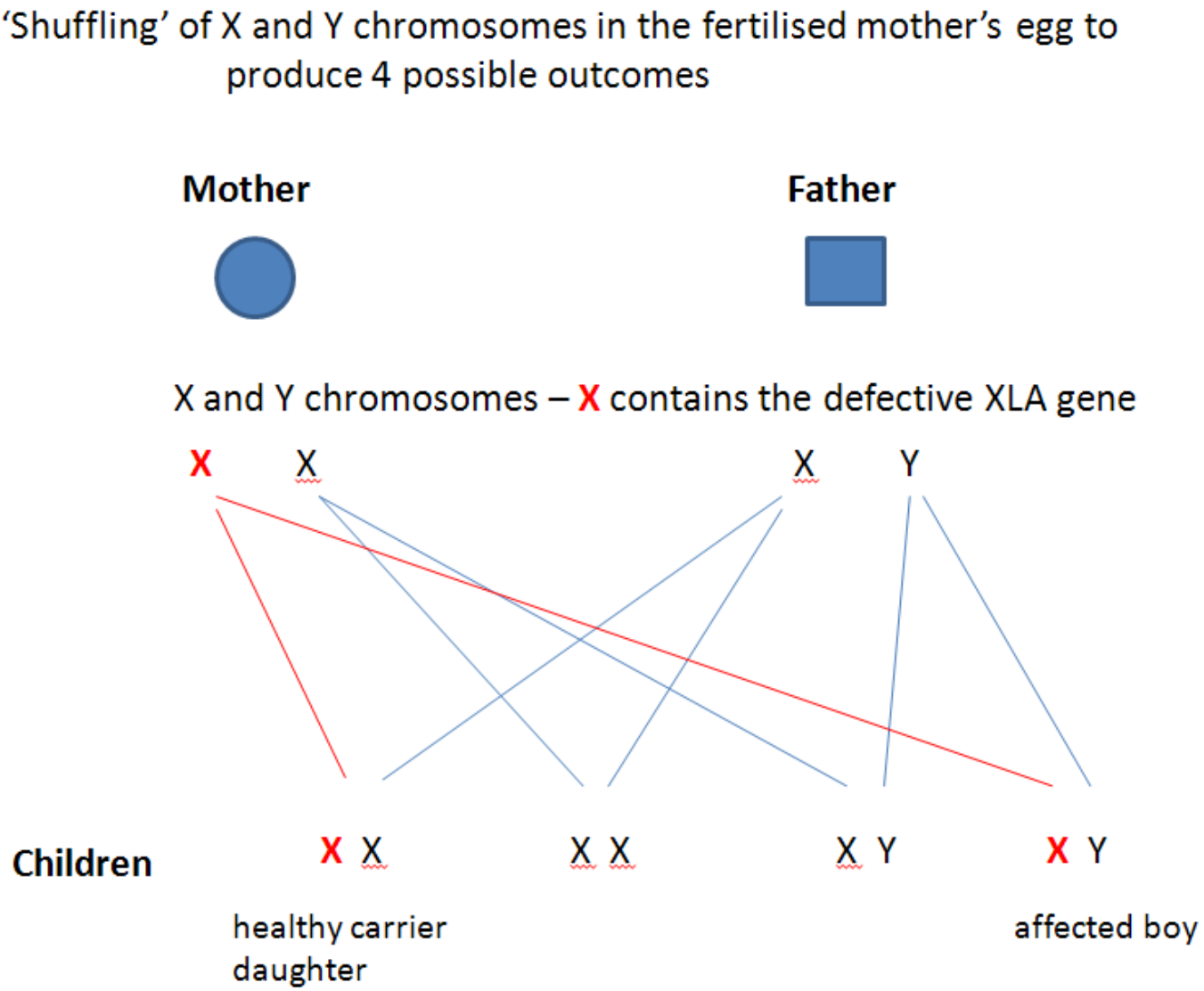
The key issue in managing the disease is to make the diagnosis as early as possible, and before infections have damaged various organs, particularly the lungs. If XLA is known in a family then all members should have the opportunity to be advised by a genetic counsellor. Girls or women carrying the defective gene can nowadays be easily identified and given the choice of diagnosing the defect at the foetal stage in early pregnancy (but only if termination is being considered), or of testing a male baby at birth. XLA patients with no family history of the disease were often mistakenly diagnosed as having another type of PID, usually CVID, although most PID clinics will now screen for XLA in all males with childhood onset severe antibody deficiency.

Once diagnosed the mainstay of treatment is regular immunoglobulin therapy, usually given every 3-4 weeks intravenously (IVIG therapy) or subcutaneously every week, the exact regime and dose being tailored individually to offer the best protection against infection. This treatment is effective and will allow most patients to lead a normal life.

As in all patients with different types of severe antibody deficiency, vaccination against infections is not useful, and vaccines that contain live microbes should be avoided.

XLA patients are susceptible to a well-recognised list of infections that cause problems in the sinuses and lungs, the bowel and less frequently the joints, bladder or brain. Some of these infections are easy to diagnose while others require tests done in special laboratories before the appropriate treatment can start. Fortunately most of the difficult to diagnose infections have become much rarer in XLA patients living in western countries over the past 20 years because the standard dose of immunoglobulin therapy has been increased. Nevertheless there is no room for complacency and patients should have confidence that their specialist has the necessary experience of XLA to know what tests are needed. In general, the earlier in life immunoglobulin treatment is started the better, as any permanent damage to the lungs from infection will increase the chances of further infection, and damage to joints or brain might be irreversible.

What of the future? XLA should be an ideal disease to cure with gene therapy or bone marrow stem cell transplantation. Although major advances are being made in correcting gene defects or replacing bone marrow in more severe and life-threatening PIDs, these procedures still carry too much risk for most XLA patients who generally do well if managed properly. However we may take a very different view in 10 years time.



A Patient's story

X-linked agammaglobulinaemia (XLA)

I was diagnosed with XLA in 1993 when I was in my early forties. My job as a manager at my local hospital brought me into daily contact with medical staff and one day a Chest Physician pointed out that I seemed to suffer from a cough and cold almost continuously which was not normal, so he arranged for me to see other consultants for tests. You should remember that XLA was not recognised until the 1950s and is so rare that only a few GPs will ever encounter it. I was treated with antibiotics and told that I had a weak chest and should take care of myself! However, I became increasingly aware that the infections were getting worse and I was taking longer to recover. I almost missed my wedding as I went down with flu just days before.

When I was given the results of the tests, I did not understand what I was being told. I only heard the words Immune Deficiency and immediately thought I had contracted AIDS. Many of you will remember that in the late 80s and early 90s AIDS was constantly in the headlines as the new scourge with no cure. Even though I worked in a hospital I did not appreciate the difference between a Primary Immune Deficiency (PID) and an Acquired Immune Deficiency like AIDS caused by the HIV virus. I was in a state of shock and wondering how to explain this to my wife and family. It was only when I started to receive treatment at a specialist Centre, which was then at Northwick Park Hospital, that Dr. David Webster and his colleagues were able to explain what I had and what could be done about it.

Looking back, it was obvious that I was a classic case. My first major infection was at 6 months old. Thereafter I had frequent coughs and colds, and throughout my early teens had a succession of major chest infections including bronchitis, pneumonia and pleurisy. The explanations from the PID specialist team put everything into context. However, it was still a shock to learn that I had what was probably a hereditary condition that was manageable but not curable. The thought of life-long treatment which provided maintenance but no cure was not very inviting. My family were not particularly happy that they needed to be tested to see if anybody else had it and were all relieved that none did. By that time, and with my mother already dead, it was impossible to determine how I had inherited the defect.

The biggest issue my wife and I had to face was what to do about having a family. We had been married only four years when I was diagnosed and whilst we had not actively discussed having a family, there was an expectation from our relatives that we would get round to it in due course. Given that XLA can be hereditary, a serious discussion was required on what to do. The consultant who looked after me at my local hospital said that the pregnancy could be "managed" and both my wife and I knew what that meant. We decided that we would not have children and have concentrated on pets instead!

So, how am I now 20 years after diagnosis? Well I am still working at my hospital, doing long stressful hours, although about to retire. I have my immunoglobulin infusions every three weeks at the hospital where I work. Most of the people I work with know I have regular treatment and are very supportive, although they probably do not know why I need this treatment. I even refer to the infusion time as a chance to catch up on paperwork and to interact with other patients in my hospital! Yes I still get infections but they are generally not as extreme. In fact, when I meet other PID patients I almost feel a bit of a fraud because some seem to have a more severe disease. My GP has little involvement in my care and it is fair to say that after 20 years I probably know more than he does about the condition. As there are only about 100 patients in England with XLA, few GPs would ever have any experience of treating it, and therefore my care is mainly hospital based. I recognise that there are places in the world that I would love to visit but will probably never get to because of the health risk. I also realise that I am unlikely to live to a ripe old age and will never be cured. I cannot influence that, so like so many other PID patients I just get on with it and live as normal a life as possible.