

LIVING WITH X-LINKED AGAMMAGLOBULINEMIA (XLA) IN A DEVELOPING COUNTRY SETTING: CLINICAL AND COUNSELLING CONSIDERATIONS IN AN AFFECTED FAMILY

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ABSTRACT

Introduction: X-linked agammaglobulinemia (XLA) is the prototype of humoral primary immunodeficiency disorders. Although the prognosis has improved in recent years, the outcome still varies in different social settings. We describe the clinical burden of XLA, the impact of living with it, and the role of genetic counselling for a family managed at Tygerberg Hospital.

Methods: Data was collected from clinical case notes and through semi-structured qualitative interviews with family members. A detailed pedigree of the family was used to highlight important clinical and genetic counselling considerations.

Results: Factors that may result in the poor outcome in some members of this family included low socio-economic status and higher exposure to infection, delayed diagnosis, lack of adherence to intravenous immunoglobulin prophylaxis in adolescence and adulthood, irregular follow-up at the Clinical Immunology Service, and poor understanding of the condition. The high burden of disease and early death of affected individuals resulted in fear of the condition, and difficulties in communicating and adjusting to the diagnosis.

Conclusion: Primary immunodeficiency disorders, such as XLA, have a dramatic impact on the lives of affected individuals and families in a developing world setting. Genetic counselling has an important role to play in the comprehensive management of these families.

INTRODUCTION

X-linked agammaglobulinaemia (XLA), also known as Bruton's agammaglobulinaemia is the prototype humoral primary immunodeficiency disorder (PID) and the first well publicised description and simultaneous treatment of a PID. It is characterised by the absence or very low numbers of circulating mature B-cells, reduced levels of all serum immunoglobulins and the lack of specific antibody production. Mutations in the gene responsible for the Bruton's tyrosine kinase (BTK) enzyme result in defective maturation of developing B cells. Expression of BTK protein is deficient on flow cytometry, but since protein expression may be normal in XLA clinical phenotype and as a wide variation of severity of clinical symptoms has been observed due to 'leaky' defects, the diagnosis by BTK gene analysis remains definitive.

The BTK locus is at Xq22.1, and XLA is inherited in an X-linked recessive manner.¹ This inheritance pattern has particularly important familial implications, and should be well understood by clinical immunologists because it is a common pattern across a range of PIDs.

Males with XLA are very susceptible to respiratory infections with encapsulated bacteria from late infancy or early childhood, at the time that the levels of passively acquired maternal antibodies decline. In addition, meningococcal meningitis with enteroviral infections can be serious and difficult to prevent or treat, and gastrointestinal infection is a common feature. With a good socio-economic background and ready access to healthcare, the diagnosis may even be delayed into mid or later childhood.

Early diagnosis and initiation of treatment is essential to prevent morbidity and mortality. Treatment is aimed at preventing lung damage and involves lifelong replacement with high level immunoglobulin either intravenous (IVIG) or subcutaneous (SQIG), as well as avoidance of live-attenuated vaccines. As mucosal immunity cannot be replenished, prophylactic antibiotics may be indicated as well. The prognosis for affected individuals has improved dramatically over the last 20-30 years,² but still varies greatly in different social settings. The long-term prognosis is dependent on awareness of disease, access to care, and diligent follow-up and monitoring.³

Tygerberg Hospital in Cape Town, South Africa is a public health facility that serves as a tertiary referral centre for a wide area of the Western Cape. Individuals affected with or suspected of having PIDs, such as XLA, are referred to Tygerberg Hospital for diagnosis and management from the Western Cape and beyond. Affected individuals are seen by a specialist clinical immunology service to establish a diagnosis and thereafter every 3-6 months to monitor health status and medical management, e.g. immunoglobulin levels.

Since 2012, affected individuals and their families are also offered dedicated genetic counselling. This adds an important component of comprehensive care for patients and their families. Genetic counselling assists families in understanding the cause and inheritance pattern of the condition and empowers them with information on the condition. Genetic counselling includes a discussion on recurrence risk implications and the identification of at-risk female carriers in particular, and facilitates genetic testing in families where the disease-causing mutation is known. Testing may be for diagnostic purposes, for carrier testing in at-risk female relatives or possibly for prenatal diagnosis of an affected pregnancy. Genetic counselling also addresses reproductive decision-making and provides the opportunity for psychosocial support.^{4,5}

This article aims to describe a large family affected with XLA from a rural town in the Western Cape, referred to and managed at our clinic. The clinical burden of the condition, the role of genetic counselling and the impact of living with XLA in the family, are discussed.

METHODS

Background: We describe an extended family including several members affected with XLA. The disease-causing mutation in this family was initially identified by Pienaar et al. (2000) as a 3bp deletion in exon 3 of the BTK gene, resulting in loss of a single amino acid (lysine).⁶ Many family members received genetic testing as part of the initial research, but a diagnostic test for the family-specific mutation has recently been established at our institution, and several individuals have received subsequent diagnostic or carrier testing.

Data collection: Data was gathered from clinical case records of the Immunology Clinic, of genetic counselling outpatient visits and of admission notes for affected individuals at Tygerberg Hospital. In addition, semi-structured qualitative interviews were conducted with mothers of four of the affected boys in the family.

Data analysis: Interview data and notes were analysed using descriptive content analysis. Interviews were transcribed and read and re-read to identify emerging themes.

Ethics: Ethical approval for this study was obtained from the Research Ethics Committee of the University of Stellenbosch (No: N13/05/075).

RESULTS

FAMILY HISTORY

A detailed pedigree of the family is presented in Figure 1. There were nine affected boys in the family, five of whom have passed away from the condition. There were 10 known female carriers (carrier status had been confirmed molecularly in nine cases, with one being an obligate but untested carrier). One of the affected boys (IV:14) was adopted, and had no ongoing contact with the biological family - his diagnosis was only communicated after the adoption procedures had been completed.

CLINICAL OUTCOMES

The available clinical details on the affected individuals are provided in Table I. The two affected males in generation III died at 18 months and 9 years of age, respectively. Three of the seven affected males in generation IV were deceased, at ages 12, 20 and 27 years. Of the four living affected males, two (IV:18 and IV:19) were identical twins who were raised in a single large household, comprising 19 members of the extended family. The twins had had recurrent infections, growth stunting and chronic health problems.

The youngest affected living member of the family (IV:23) was 4 years old and currently healthy. He lived separately from the large household. The oldest survivor (IV:14) was adopted at a young age, and was in good health at 29 years of age. His only biological brother (IV:15) was the affected male who died at 20 years of age: he was raised by his biological family in the large household, and had severe, ongoing XLA-related health problems.

SOCIO-ECONOMIC CIRCUMSTANCES

Most family members lived in a rural town, approximately 100 km from Tygerberg Hospital. As described, until recently 19 individuals from this family were all living on one property, in poor socio-economic circumstances. With individual II:7, four of her daughters and all of their children were living in the main house which had a single bathroom. Two of the daughters stayed in two small prefabricated wooden houses (Wendy houses) at the back of the property, which had no

running water. They used buckets for sanitation, because of their limited access to the single flush toilet and clean running water inside the main house. The affected twin boys lived in one of these Wendy houses, but had recently moved to an independent apartment in the nearby town. The other two affected boys who lived on this property died from infection-related causes at 27 and 20 years of age, respectively.

The 4 year old affected boy (IV:23) came from middle class circumstances. He lived with his mother (III:15) and grandmother (II:9) in a two-bedroomed, one-bathroom house just a few streets away from the above-mentioned family in the same town. His mother was unmarried and employed full-time. They had very little contact with the rest of the family.

The adopted boy also grew up in significantly better socio-economic circumstances compared to his sibling and cousins. His father had regular employment and a private medical health insurance. He grew up as the single child of the family. Medical care was accessible, follow-up with immunoglobulin infusions was diligent and any infections were attended to promptly. He has not suffered any serious infections during the course of his 29 years of life. He had developed normally, led a healthy, productive, economically independent life with fulltime employment in a clerical position. He had chosen to self-infuse his IVIG at home.

THEMES IDENTIFIED IN INTERVIEWS

Semi-structured interviews were conducted with individuals III:8, III:9, III:10 and III:15. Themes identified using content analysis are presented in Table II, together with related quotes and responses.

DISCUSSION

CLINICAL BURDEN OF DISEASE AND POSSIBLE FACTORS IN POOR OUTCOME

With early detection and correct management, XLA should have a good prognosis.⁷ Soresina et al. (2009) found that a group of children and adolescents with XLA in Italy had a self-reported health-related quality of life similar to healthy controls.⁸ Howard et al. (2006) reported on 41 American adults living with XLA and found that the majority were doing well and living productive lives.⁹ The vast majority were either employed or full-time students, with very few hospital admissions and quality of life comparable to healthy peers. Similarly, Winkelstein et al. (2008) reported a quality of life comparable to the general population in a group of American adults with XLA.¹⁰

The prognosis for affected individuals in the family we describe has been relatively poor, as illustrated by the death of five out of nine of the affected individuals at young ages. Recurrent infections, frequent hospital admissions, failure to thrive and stunting of growth were characteristic features of the condition in the majority of the affected boys in this family. Nevertheless, survival appears to have improved between generation III and IV, perhaps related to earlier diagnosis and

improved treatment.

We identified several possible factors which could explain the differences in outcome between the different affected individuals in the family, and between our family cohort and the literature. These include poor socio-economic circumstances, delayed diagnosis, lack of proper follow-up and poor understanding and awareness of the condition and adherence problems with treatment.

Socio-economic circumstances: A striking difference was observed in the two affected brothers who grew up in different environments. They shared the same disease-causing mutation, but their progression of disease and outcome had been very different. The adoptee had maintained a good quality of life, similar to that described for affected individuals in developed countries. Similarly, the more recently diagnosed 4 year old cousin living in better economic circumstances had had few infections and normal growth, despite not receiving IVIG until his relatively late diagnosis.

Household crowding and large family size are a known risk factor for respiratory infections in childhood even without immune deficiency,^{11,12} presumably because they facilitate the spread of respiratory pathogens. Good hand washing and excreta disposal are estimated to reduce the frequency of childhood diarrhoeal disease by 48% and 36% respectively.¹³ The fact that 19 members of this family lived in crowded and relatively insanitary circumstances exposed affected males to additional risk of respiratory and gastrointestinal infections.

Diagnosis: Early diagnosis is important since immunoglobulin replacement is effective in preventing severe bacterial infections and limiting resultant complications such as bronchiectasis.³ For most affected males in this family diagnosis was preceded by symptoms and took place relatively late, after 2 years of age, although two of the more recently born boys were diagnosed within the first 6 months of life (Table I).

Treatment and adherence: All of the affected family members who received IVIG (Table I) have had access to regular immunoglobulin treatment at a nearby hospital for many years. In general, they were adherent to treatment in childhood, but often had suboptimal follow up during the transition from childhood to adolescence and during adulthood. This reflects lack of awareness of PIDs by medical practitioners caring for older patients with these conditions, but adherence issues must also be considered in adolescents with chronic diseases.

Even in childhood, attendance of the Immunology Clinic for monitoring was sub-optimal. This can be ascribed largely to the fact that the clinic was at Tygerberg Hospital, 100 km from the residence of most family members. This was a particular problem for family members in the large household,

as they were dependent on transport provided by the local hospital.

Affected boys missed school one day every three weeks to receive IVIG treatment, and an additional day every third month to attend their Tygerberg Hospital appointment. Although they were frequently kept at home for infections, family members did not feel that the condition had a major negative impact on schooling. Studies in developed countries have found similar findings. Soresina et al. (2009) found that XLA did not have a significant impact on school functioning in a group of Italian patients with XLA.⁸ Winkelstein et al. (2008) reported that XLA had an impact on the daily lives of affected individuals, in terms of missing school or work, but despite this, found a socio-economic status and quality of life comparable to the general population.¹⁰

In contrast to the other affected family members, the adopted male self-administered his immunoglobulin treatment intravenously at home and rarely needed to miss school or work for health-related reasons. In the Winkelstein study, 70% of affected individuals self-administered IVIG. The increasing use of subcutaneous route of globulin administration may help prevent school and work loss in future.¹⁰

IMPACT OF THE CONDITION ON THE FAMILY

Content analysis of the interviews with mothers of affected children identified the themes of practical and psychosocial impact of the condition, especially in the large household. At a practical level, frequent hospital visits and recurrent hospital admissions had become part of everyday life. Some mothers of the affected children were unable to work because of caring for their affected sons, as illustrated in Table II. This put additional financial strain on already resource con-

strained circumstances.

In the large household, the psychosocial effects related in part to the deaths of several affected individuals. This family had no contact with the healthy adopted boy and their only frame of reference was that affected individuals did not survive beyond their 20's. Mothers' experienced great sadness and longing with the loss of the affected children.

Affected males and family members in the large household feared the condition, which was seen as an inevitable progression of disease and death. Unlike other families, they described knowing that their children would die young and also how they would die. One of the mothers of the affected boys (III:6) who had passed away, recalled her son (IV:9) telling them often that each time he went to bed he feared that he may not wake up (Table II).

With the twins approaching their 20's, it was evident that the family was increasingly worried and anxious how their disease might progress. Kuburovic et al. (2014) found that particularly anxiety and symptoms of depression were more common amongst children with PIDs and their parents, compared to healthy peers.¹⁴ Other studies have also reported an increase in psychological issues, such as anxiety and depression amongst parents of children with chronic illness.¹⁵ This family dreaded the condition with each new male addition to the family. Despite being reassured by the medical professionals caring for the family that individual V:6 had been tested and was unaffected, the family remained concerned about him, because he resembled the affected boys.

Fear of the condition had resulted in poor communication about the condition in the family. The condition was not discussed within the family and at-risk females had often not

TABLE I: CLINICAL DATA FOR MALES WITH X-LINKED AGAMMAGLOBULINAEMIA

PEDIGREE POSITION	YEAR OF BIRTH	AGE AT DIAGNOSIS	B CELLS	MUTATION	OUTCOME
III:5	Unknown	Unknown	NA	NA	Deceased age 18 months
III:12	Unknown	Unknown	NA	NA	Deceased age 9 years
IV:7	Unknown	Unknown	NA	NA	Deceased age 12 years
IV:9	1981	2 years	0%	Yes	Initial IM IgG replacement, lost to follow up during adolescent transition, bronchiectasis, chronic renal and hepatic failure, severely stunted. Deceased age 27 years
IV:14	1985	2 years	2%	Yes	Healthy on IVIG
IV:15	1991	15 months	0%	Yes	Encephalitis in childhood, severe cerebral palsy. Seizures. Hepatitis. Deceased age 20 years, despite replacement IVIG
IV:18	1996	6 months	<1%	Yes	Persistent fungal UTI post circumcision, tuberculosis infection of ear, recurrent Giardiasis and Campylobacter enteritis infection, stunted but clinically healthy on IVIG
IV:19	1996	3 months	<1%	Yes	Recurrent Giardiasis and Campylobacter enteritis infection, stunted, chronic hepatitis, on IVIG
IV:23	2010	2 years	0%	Yes	Healthy on IVIG

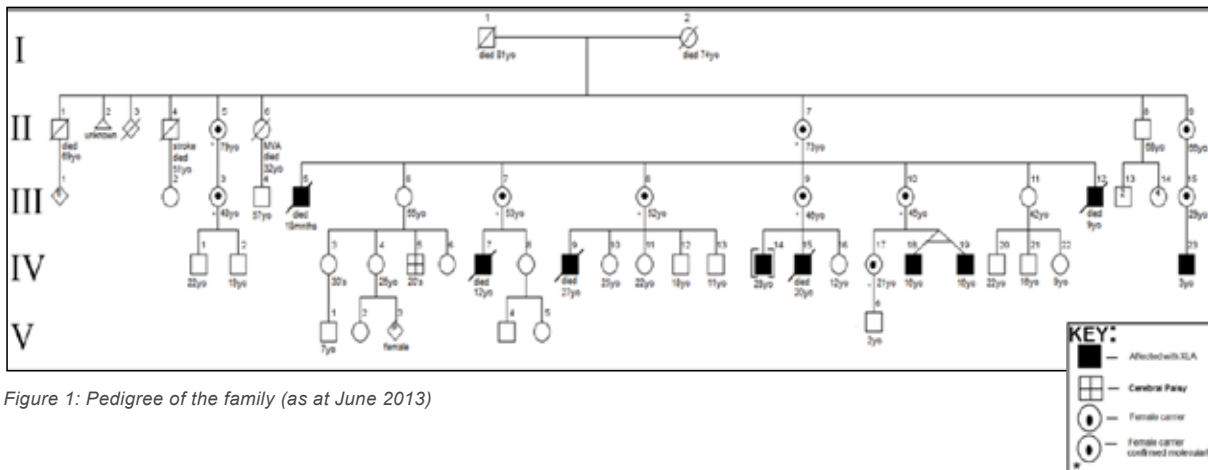


Figure 1: Pedigree of the family (as at June 2013)

been informed of their carrier risk by their mothers, which was important to facilitate genetic counselling and ‘cascade testing’ of at-risk family members. Despite the significant number of affected individuals in the family, individual III:15 (mother of the youngest and most recently diagnosed boy in the family), was unaware that XLA was a condition that ran in the family and that she was at risk of having an affected child. She came from better socio-economic circumstances than the majority of her family and had very little contact with them. Although she knew there were sick boys in the family, she did not think it could affect her life or that of her children.

For risk information to be distributed in a family, knowledge and understanding of genetic risk is essential.¹⁶ Studies have shown that risk information is often not communicated in families, for reasons such as the overall pattern of family communication, including family rules, roles and beliefs, social class, geographical and emotional distancing and the individual coping styles of family members.^{17,18} It is essential that healthcare providers recognise this.

This same individual (III:15), with a very good level of education and better socio-economic circumstances than the majority of her family, remained in denial about the diagnosis in her son, despite clinical confirmation and symptoms as proof that he was affected, as well as several visits to the clinical immunologist. Molecular confirmation that she was a carrier of XLA and

that her son carried the disease-causing BTK mutation had since been provided to her. This had helped her consider the diagnosis but she was still struggling to accept it.

Denial is a powerful psychological defence mechanism, and is used to protect the individual from anxiety and other emotions until they can face reality.^{18,19} However, denial can have significant negative effects on knowledge and use of medical care. While it may be counterproductive to challenge denial, it is important that individuals experiencing denial are followed up in a supportive environment to facilitate adaptation to the diagnosis, and to identify responses that warrant intervention.¹⁹ Genetic counselling is the ideal setting in which to do this.

GENETIC KNOWLEDGE AND GENETIC COUNSELLING

The majority of this family still had limited access to information and scientific resources and no internet facility. They were therefore dependent solely on the medical and genetic information provided to them by their health care professionals.

Genetic counselling in this family included obtaining further details of family history and extending the pedigree, repeatedly explaining the genetic cause of the condition, the X-linked inheritance pattern, recurrence risks and implications for the family. The X-linked inheritance pattern and the 50% risk of carrier females having affected sons, had significant implications

TABLE II: THEMES IDENTIFIED FROM INTERVIEWS WITH MOTHERS OF AFFECTED BOYS

THEME	QUOTES/RESPONSES OF INTERVIEWEES
Practical impact - frequency of hospital admissions	III:9 "I always made my bed on the floor in the hospital. It was like a home to me, we were there so often." III:8 "Eventually I realised my child is more important now, his health, I need to be at home now for him."
Psychosocial impact - grief	III:8 "Our kids were there for us, given to us, but they have been taken away from us."
Psychosocial impact - anxiety	Several "our children will die young" ...and... "not at home, but in a hospital bed, because of this condition." III:8 quoting her deceased son IV:9 "you can close your eyes tonight and you know you will be opening them again tomorrow morning. But I have a risk, I can go to sleep tonight, but I don't know if I will be opening my eyes tomorrow."
Variable knowledge about XLA	III:15 had limited knowledge, and her responses indicated that she was in denial of the possibility of XLA in her son
Limited communication about familial implications of XLA	Responses suggest that limited communication is related to fear of the condition

for the maternal line of this family. Identification of at-risk female relatives allowed them to be offered carrier testing, as well as prenatal diagnosis or diagnostic testing of children in early infancy. Genetic counselling provided an opportunity to obtain a detailed family history and to allow informed decision-making regarding genetic testing. In addition, it permitted exploration of understanding, experiences and the psychosocial impact of the condition in the family, assessment of important social issues, and reinforcement of management principles.⁵

Genetic knowledge in this family varied. Some family members were aware that females were carriers of the condition and could pass it on to their sons. Other mothers had never thought about what it meant for their daughters and also had not informed their daughters that they were at risk of having affected sons. One mother knew that she had to phone the hospital immediately if she found out one of her daughters were pregnant, but she had not informed the daughters of reproductive age that they were at risk of being carriers. There were at least four potential carrier females in this family who had not been tested. In view of the limited intra-familial communication in this family, follow-up was important to facilitate carrier testing.

The availability of family-specific genetic testing had been important for this family, but did not necessarily translate into the availability of genetic testing for other affected families since most disease-causing mutations are unique to each family. There is a need for more comprehensive genetic testing of XLA, e.g. full gene sequencing, to be made locally available. However, despite the increasing availability of next-generation sequencing techniques, the rarity of the condition and the complexities of interpreting even relatively straight-forward genomic

data remains a challenge for clinically useful implementation.

CONCLUSION

Primary immunodeficiency disorders, such as XLA, have a dramatic impact on the lives of the affected individuals and their families, with even greater challenges being faced in a developing country setting. Specific challenges in this family related to early death of affected individuals and burden of disease. This resulted in fear of the condition and difficulties in communicating about, and adjusting to the diagnosis. Several factors were identified that may account for the variable or poor prognosis in this family, including higher infection exposure related to poor socio-economic circumstances and especially household crowding and poor sanitation, delayed/late diagnosis, and lack of adherence to treatment especially after childhood. Increasing awareness and knowledge of PIDs among the medical profession, especially during the transfer from paediatric to adult care, is essential for improved outcome.

Genetic knowledge was variable in this family, and communication regarding the diagnosis and implications was limited. Genetic counselling has a crucial role to play in the comprehensive management of families affected by PIDs, by empowering them with information about the condition, facilitating genetic testing and by offering psychosocial support. It should therefore be offered as part of standard care.

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DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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