

The health status and quality of life of adults with X-linked agammaglobulinemia

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Abstract

Forty-one adults (mean age 33) with a definitive diagnosis of X-linked agammaglobulinemia (XLA) completed a questionnaire concerning current and past medical problems and quality of life. Thirty-six of the 41 were working full time or were full time students; 18 had not missed any work or school due to infection in the previous year. Their quality of life was equivalent to that of the general US male population. Thirteen of the 41 reported that they had chronic lung disease, and 33 indicated that they had one or more episodes of sinusitis in the preceding year. Arthritis, diarrhea and skin infections were common but not debilitating. The 41 study subjects were more likely to have a prior family history of XLA, and they were more likely to have milder mutations in Btk, the gene responsible for XLA. These results indicate that most adults with XLA are moderately healthy and lead productive lives.

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Introduction

X-linked agammaglobulinemia (XLA) is a rare genetic disorder of the immune system resulting in the early onset of recurrent infections, profound hypogammaglobulinemia and markedly decreased or absent B cells [1–6]. The patients are most vulnerable to infections with encapsulated bacteria, particularly *S. pneumoniae* and *H. influenzae*, and they generally begin to have frequent episodes of otitis by 4 to 8 months of life. The majority of patients with XLA are

recognized to have immunodeficiency at less than 5 years of age when they are hospitalized for severe infection [7]. Currently, patients are treated with aggressive use of antibiotics and monthly infusions of intravenous gammaglobulin, a therapy that became widely available in the mid-1980s. Prior to that time, patients were treated with intramuscular injections of gammaglobulin or plasma therapy, neither of which provided optimal amounts of gammaglobulin.

Recurrent pneumonias, otitis and sinusitis in patients with XLA have been reported to cause chronic lung disease and hearing loss [2,8,9]. In addition to their increased susceptibility to infections with encapsulated bacteria, patients with XLA have an elevated risk of infection with giardia, mycoplasma and enteroviruses [10–14]. Giardia infections in these patients are sometimes associated with the development of inflammatory bowel disease. Chronic pneumonitis and/or arthritis can result from infection with mycoplasmas [12]. Most viral infections do

Abbreviations: XLA, X-linked agammaglobulinemia; BMI, body mass index.

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not cause unusual problems in patients with XLA; however, the enteroviruses, including echo virus, coxsackie and wild type and vaccine associated polio, can cause chronic, progressive, devastating enteroviral meningoencephalitis, arthritis or enteritis [13–18]. In the late 1980s and early 1990s, some patients with XLA acquired hepatitis C through contaminated preparations of intravenous gammaglobulin [19–21]. Because hepatitis C infection can remain asymptomatic for 10 to 20 years, the long-term outlook for these patients has been uncertain.

XLA was first described by Bruton in 1952 [1], and, between 1950 and 1980, most affected patients died at less than 20 years of age. Some patients died of their first major infection, about 20% died of chronic enteroviral infection and a significant proportion died of chronic lung disease or cor pulmonale secondary to chronic lung disease [2]. In 1985, Lederman and Winkelstein published a comprehensive survey of 96 patients with XLA [2]. Sixteen of the patients died at a mean of 17 years of age, and the oldest patient was 28 years old. In that series, 41% of patients between 10 and 20 years of age and 76% of patients over 20 years of age had chronic lung disease. In a more recent study, Plebani et al. reported that 80% of patients who had been followed more than 17 years had chronic lung disease [4]. Because of improvements in diagnosis and therapy in the last 20 to 30 years, an increasing number of patients with XLA are now surviving into adulthood; however, other than case reports, there is very little information in the medical literature about the health status of adults with XLA.

In 1993 two groups demonstrated that XLA was caused by mutations in a hematopoietic-specific signal transduction molecule called Btk (for Bruton's tyrosine kinase) [22,23]. In addition to clarifying the requirements for normal B cell development, this finding made it possible to make a definitive diagnosis of XLA in patients with atypical findings and to exclude the diagnosis of XLA in individuals who had clinical findings similar to those seen in XLA. To determine the health status and quality of life of adults with a definitive diagnosis of XLA, we asked adults with proven mutations in Btk to fill out a questionnaire that addressed past and current medical problems, psycho-social functioning, employment status and financial concerns.

Materials and methods

Survey

The 16-page survey included questions about family history, past medical history, current medical problems, current therapy, dyspnea as measured by the MRC dyspnea scale [24], quality of life as measured by the SF-12 (SF-12v2, 4 week recall) [25] and marital, financial, employment and insurance status. The form of the survey included yes or no questions, multiple choice questions, fill in the blanks and free text.

Study subjects

The entry criteria for this study were: (1) a definitive diagnosis of XLA as documented by markedly reduced numbers

of peripheral blood B cells (less than 2% CD19+ B cells) and one of the following: a proven mutation in Btk, absent Btk in monocytes or platelets or maternal cousins, uncles or nephews with less than 2% CD19+ B cells [26]; (2) birth date before August 13, 1982; and (3) fluent in English. The study subjects were recruited from patients under our care and from families that had participated in previous research studies examining the genetic etiology of B cell deficiency. Some clinical information about the latter patients had been obtained from the referring physician or genetic counselor as part of the research studies, which have been ongoing for 20 years. Potential study subjects were contacted by telephone and invited to participate. The survey and a consent form, along with return envelopes, were sent to individuals who agreed to take part in the study. If an individual had not returned the survey in 3 to 6 weeks, they were given a reminder. This study was approved by the St. Jude Children's Research Hospital IRB.

Statistical analysis

For subjects with and without chronic lung disease, distributions of age at diagnosis and current age were compared using Wilcoxon–Mann–Whitney test. The same two groups were compared with respect to prior family history of XLA, history of pneumonia before diagnosis, prophylactic antibiotic use, problems with sinusitis and dyspnea using Fisher's Exact test. Assuming that the 199 independently occurring mutations in Btk form the entire population, Exact Binomial test was used to test if the proportions of mutations in the study group significantly differed from the entire population.

Quality of life scores in eight areas and the overall physical and mental scores were calculated based on the SF-12 manual. Then, one-sample *z* test was used to compare our cohort with the general US male population or the US population with allergies or diabetes. To internally compare the overall physical and mental quality of life scores in various sub-groups in our XLA cohort, Wilcoxon–Mann–Whitney test was used. Version 9.0 of SAS® Software package was used in all analyses. No multiplicity corrections to the significance levels were made.

Results

Characteristics of the study population

A total of 87 adults with a definitive diagnosis of XLA were identified as potential subjects for our survey-based study. By contacting the patients, family members of the patients or the referring physicians, we were able to determine that 69 subjects were living and 9 had died at greater than 21 years of age. One subject died after completing the survey. Nine subjects could not be traced. The cause of death, the age of the subject at the time of death and the year of death for the ten individuals who died are indicated in [Table 1](#).

Of the 69 living subjects, 53 were contacted by telephone and agreed to participate in the study, and 41 returned a completed survey. These 41 individuals did not differ significantly from the

Table 1
Cause of death in adults with XLA

Cause of death	Age at death (in years)	Year of death
Perforated bowel	38	1990
Chronic lung disease	45	1993
Recreational drug overdose	25	1994
Liver failure; hepatitis C	33	1996
Enteroviral encephalitis	23	1997
Liver failure; hepatitis C	29	1999
Liver failure; Tylenol toxicity	32	2001
T cell lymphoma	25	2002
Chronic lung disease	37	2003
Peritonitis; hepatitis C; chronic lung disease	36	2004

larger group in percent belonging to a minority group (10% vs. 16%) or in percent who were full time employees or students (88% vs. 87%). The 41 study subjects were members of 32 unrelated families; they received their care from 31 different medical centers and resided in 19 different states.

The mean age at diagnosis for the 41 study subjects was 4 years (median 7.5 years, range 1 month to 53 years), and the mean current age was 33 years (median 32; range 21 to 63). The majority of the subjects (78%) were less than 40 years old. Fourteen of the 41 study subjects were the first member of their family to be diagnosed as having XLA; the remaining 27 patients had a prior family history of disease. Four of the study participants, including the 3 oldest subjects, were diagnosed as having XLA at greater than 21 years of age, after a nephew or grandson was found to have XLA. If those four individuals are excluded, the 23 subjects with a prior family history of XLA were diagnosed at a mean of 3.1 years of age. The 14 individuals without a prior history of XLA were recognized as having XLA at a mean of 5.8 years of age.

Mutations in *Btk*

To determine if the patients with XLA who survived into adulthood represented a subset of patients with milder mutations in *Btk*, the gene responsible for XLA, the specific mutations in the 41 study subjects were compared with those documented in 199 unrelated families analyzed in our laboratory [5]. As shown in Table 2, study subjects demonstrated an increased proportion of splice defects and a decreased proportion of frameshift mutations compared to the mutations seen in unselected patients with XLA. Furthermore, a high proportion of the splice site mutations in the study subjects occurred at sites that are conserved but not invariant in the splice consensus sequence, sites that are associated with milder disease [27].

Treatment for XLA

One subject, a 57-year-old man who was recognized to have XLA at 53 years of age when his grandson was diagnosed as having XLA, has never received gammaglobulin replacement therapy. This man had polio as a child, and he has had frequent

sinusitis and conjunctivitis and 5 episodes of pneumonia, but his survey did not indicate that he had chronic lung disease, a chronic cough or dyspnea. The remaining 40 subjects were receiving intravenous gammaglobulin every 2 to 4 weeks. Twenty-three of the 40 subjects (58%) were infused at home, and 5 of these 23 subjects self-infused the medication; the remaining 17 individuals received intravenous gammaglobulin in a doctor's office or an infusion center. Thirty-nine percent of patients were taking chronic prophylactic antibiotics, and 54% had taken chronic antibiotics for at least 2 years in the past. Five of the subjects indicated that they had used alternative therapies including oral colostrum, stress reduction techniques and herbal medicines.

General health

The majority of the adults with XLA have not had major problems. Forty one percent (17/41) had not been hospitalized for infection since diagnosis, and 68% (28/41) had not been hospitalized in the last 5 years. The age at diagnosis was similar in the subjects who had and had not been hospitalized since diagnosis; however, the current age of the subjects who had not been hospitalized was younger (mean 28 years, range 21–48 versus mean of 37 years with a range of 21–63 years for patients who had been hospitalized). Two subjects in their late 30s had never worked. One of these individuals reported chronic lung disease, 6–10 pneumonias in the last year and severe dyspnea. The other has not worked so that he can maintain his disability status. One subject, a 43-year-old man, had not been employed for 3 years because of a back injury sustained at work. Two subjects had been out of work for less than a year. One of these was a man in his 20s who was between jobs; the other was a 36-year-old man with chronic lung disease, hepatitis C and ascites who was not able to work because of his health. This man died after completing the survey.

Most of the subjects (83%) rated their health as good, very good or excellent. In the last year, 86% (35/41) of the patients missed fewer than 10 days of work or school due to illness, and 44% (18/41) indicated that they had not missed any work or school. Based on CDC definitions, 18% (7/40) of the subjects were obese (BMI >30), 32% (13/40) were overweight (BMI >25) and 1 subject was underweight (BMI <17). By comparison, 40% of adults in the United States are obese, 65%

Table 2
Mutations in *Btk*

	Independently occurring mutations in <i>Btk</i> (199)	Study subjects (41)	<i>P</i> value
Amino acid substitution, number (Percentage)	68 (34%)	13 (32%)	NS
Frameshift	36 (18%)	2 (5%)	0.029
Premature stop codon	41 (20%)	8 (20%)	NS
Splice site defect	35 (18%)	14 (34%)	0.02
Conserved base pair	11/35 (5%)	8/14 (19%)	0.002
Invariant base pair	24/35 (13%)	6/14 (15%)	NS
Other	19 (10%)	4 (10%)	NS

are overweight and 1.7% are underweight [28]. Five of the subjects smoked tobacco (12%) compared to 23% of adults in the United States [29]. All five indicated that they had been told to quit smoking by a physician. The majority of the subjects, 28/41 (68%), indicated that they drank some alcohol, and 3 subjects stated that they drank an average of more than 15 g of alcohol per day. Sixty one percent of the subjects stated that they were involved in sports as children or adolescents, and 34% said that they were currently involved in sports. Only 1 of the 7 obese subjects indicated that he was involved in sports.

Major medical problems

In past reports, chronic lung disease has been the most common long-term complication in patients with XLA [2,4,8,9]. In our study, 9 of the 41 subjects stated that they had been told that they had chronic lung disease, and an additional 4 indicated that they had permanent loss of lung function due to XLA (13 subjects). Three of the four men who were diagnosed as having XLA as adults reported that they had chronic lung disease.

The 13 individuals reporting chronic lung disease were older (mean age 40, range 23–63) than those without chronic lung disease (mean age 30, range of 21–57) (Table 3); however, if the four subjects diagnosed as having XLA as adults are excluded, the age at diagnosis was not statistically different in the patients with and without chronic lung disease. The two groups were equally likely to report one or more pneumonias prior to diagnosis (56% vs. 59%). All of the subjects reporting chronic lung disease indicated that they had

one or more episodes of sinusitis in the preceding year, and 2 indicated that they had sinusitis all of the time. Of these 13 subjects, 11 reported one or more episodes of cough in the preceding year and 8 stated that they coughed all of the time. None of the subjects with chronic lung disease was using oxygen. On the MRC dyspnea scale, one of the subjects who had never worked reported severe dyspnea, another subject indicated that he had moderate dyspnea and two subjects reporting chronic lung disease indicated that they had mild dyspnea. The remaining 9 subjects who reported chronic lung disease had no dyspnea. Two of the subjects who did not report chronic lung disease indicated that they had mild dyspnea. One of these subjects was obese, the other had no obvious reason for dyspnea.

In patients with XLA, chronic antibiotics may be used to prevent infection or they may be used to treat persistent infection in patients with chronic lung disease. To help determine if chronic antibiotics used to prevent infection might reduce the risk of chronic lung disease, the subjects were asked if they had ever taken daily antibiotics to prevent infection; and, if so, at what age did they start and at what age did they stop if they were no longer taking antibiotics. Subjects without chronic lung disease were slightly more likely to report the use of chronic antibiotics for at least 5 years before the age of 20; however, the difference was not statistically significant. Studies evaluating disease severity in patients with asthma or cystic fibrosis indicate that patients with low income are more disabled by their disease [30]. However, the median income of the subjects with chronic lung disease was slightly higher than those without chronic lung disease, perhaps because the individuals with lung disease were older.

Three of the 41 subjects indicated that they had hepatitis, and two specified that they had Hepatitis C. Other major problems related to XLA included chronic enteroviral encephalitis reported by one subject and an intracranial mass thought to be secondary to mycoplasma infection in another individual. As noted above, one subject had wild type polio as a child and had residual right-sided weakness requiring a leg brace. Problems that may be related to XLA included inflammatory bowel disease in one subject, disseminated herpes in another and depression necessitating hospitalization in one subject. One subject had been treated twice for colonic carcinoma and one individual had Type I diabetes.

Minor medical problems

Infections of the upper respiratory tract were common in the adults with XLA; of the patients without chronic lung disease, 20/28 (71%) reported one or more episodes of sinusitis in the preceding year and 17/28 (61%) indicated that they had episodes of cough or bronchitis; 2 said that they coughed all of the time. Small children with XLA usually have recurrent otitis media; however, only 7 (17%) of the 41 study subjects reported one or more episodes of otitis in the previous year (Table 4); however, 8 individuals indicated that they had hearing loss. Conjunctivitis was reported in 13/41 (31%) subjects. Diarrhea was reported by 8/41 (20%) of the subjects,

Table 3
Comparison of study subjects with and without chronic lung disease

	With chronic lung disease (13 subjects)	Without chronic lung disease (28 subjects)	P value
Current age in years, mean (range)	40 (23–63)	30 (21–57)	0.006
Age at diagnosis			
All subjects	10.1 (0.5–41)	6.1 (0.1–53)	NS
Excluding subjects diagnosed as adults	3.2 (0.5–13)	4.4 (0.1–12)	NS
Prior family history of XLA	10/13	17/28	NS
History of pneumonia before diagnosis	7/13	17/28	NS
Prophylactic antibiotics for >5 years at less than 20 years of age	7/13	17/28	NS
Current problems with sinusitis	13/13	20/28	0.04
Dyspnea	4/13	2/28	0.068
Severe	1	0	
Moderate	1	0	
Mild	2	2	
Median income ^a	\$75–100,000	\$50–75,000	NS

^a The study subjects were asked if their total household income before taxes fell into the following ranges (1) less than \$5000, (2) \$5000–\$14,999, (3) \$15,000–\$29,999, (4) \$30,000–\$49,999, (5) \$50,000–\$74,999, (6) \$75,000–\$99,999, (7) \$100,000 or more.

Table 4
Chronic or recurrent problems in adults with XLA^a

	All the time	6–10 times	1–5 times	Never
Sinusitis	5	6	22	6
Cough	10	2	15	11
Bronchitis	3	1	12	20
Conjunctivitis	1	2	10	22
Skin infections	2	3	6	24
Diarrhea	0	2	6	28
Ear infections	1	1	5	29
Arthritis	6	0	1	29
Pneumonia	0	1	6	26

^a The study subjects were asked to circle the estimated frequency of the listed conditions in the preceding 12 months. Some of the subjects did not circle a frequency for some conditions.

but none had lost more than 10 pounds in the preceding year. Other medical problems including arthritis and skin infections were seen in a notable proportion of subjects. Two of the subjects reported genitourinary problems, urethritis or prostatitis. Three of the subjects indicated that they had had appendectomies, and one subject had his gall bladder removed. Medical problems commonly seen in adults including hypertension (one subject) and Type II diabetes (no subjects) were rarely reported.

Cost of medical care

Forty of the 41 subjects indicated that they had health insurance. The majority, 33, were insured through their own employer or through the employer of a family member. Two had individual policies, and 5 were insured through Medicare, Medicaid or a state health program. However, 19 of the subjects noted that they had had difficulty in obtaining or maintaining insurance. Twelve had had new insurance denied, conditions excluded or coverage denied. Nine had had

treatment delayed because of insurance. Five had had health insurance cancelled; and five had reached their life-time cap. Of the 41 subjects, 14 reported that at some time they did not get the care they needed because of cost. Specifically, 10–20% of the subjects did not obtain prescriptions, did not get gammaglobulin replacement, did not see a doctor when sick, did not see a specialist or did not get prescribed tests when appropriate and approximately 5% of the subjects did not have an operation when needed or did not go to the hospital when they were having problems because of the cost. One subject accumulated a \$120,000 hospital bill when he was not insured, in the year before he completed the survey. If this subject is excluded, the mean out of pocket expense for health care was \$1388 with a median of \$500.

Quality of life

The quality of life in the study subjects was assessed by the 8 questions that constitute the SF-12. These questions focus on the individual's energy level, their emotional health, their ability to participate in routine physical and social activities, their level of pain and their perception of their general health. The results are reported as scores for each parameter and in summary scores for mental and physical health. For all parameters except perception of their general health, the adults with XLA were equivalent to the general U.S. male population. They had significantly less pain and greater vitality than subjects with allergies ($P < 0.05$). When compared with subjects with another chronic disease, diabetes, the subjects with XLA had a better quality of life in every parameter (Fig. 1).

We examined the possibility that the quality of life might be influenced by the current age of the subject, his income or type of insurance, the presence or absence of chronic lung disease, the marital status of the individual (22 were married) or whether the subject received gammaglobulin therapy at home, or in a clinic or hospital setting. The mental health, but not the

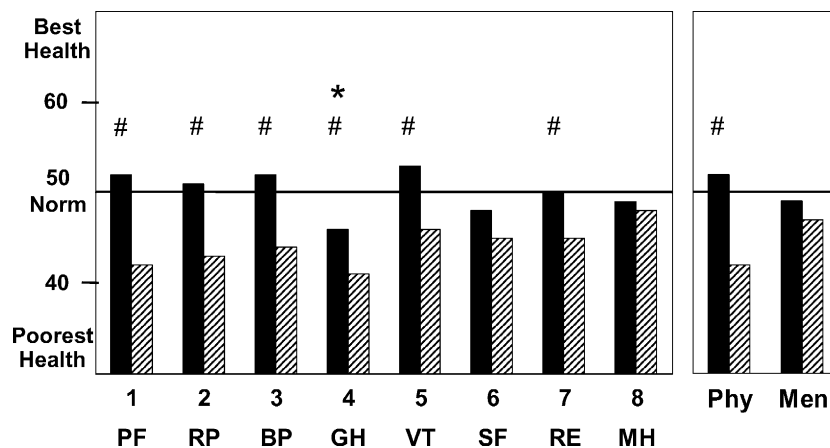


Fig. 1. Quality of life scales comparing subjects with XLA to those with diabetes. The y axis shows the score for each parameter. The score for the general US population for each parameter is 50. The parameters are numbered 1 through 8 with the standard abbreviation for each parameter. The summary scores for physical and mental health are indicated at the right. The parameters measured were: (1) physical strength; (2) physical activity; (3) bodily pain; (4) perception of general health; (5) vitality; (6) social functioning; (7) role of emotions; and (8) level of depression. The scores for the subjects with XLA are shown in black bars, those for subjects with diabetes (obtained from the SF-12 manual) are shown in hatched bars. Scores that are significantly different in subjects with XLA versus controls are indicated by *. Scores that are significantly different in subjects with XLA versus subjects with diabetes are indicated by #.

physical health, of the subjects with chronic lung disease was statistically worse ($P = 0.05$) than that of the subjects without chronic lung disease. None of the other variables was statistically associated with the quality of life.

We asked the adults with XLA how the various aspects of their lives were influenced by their disease; for each area, the subjects could indicate whether having XLA limited them not at all, a little, some or a lot. Less than 15% of the subjects indicated that having XLA affected friendships or their sex life. Approximately a third said that having XLA influenced their social activities, their ability to sleep, their participation in sports and recreation or their ability to tolerate normal physical exertion. Over half said that having XLA affected their lifestyle, their ability to travel and their career choice. Twelve of 39 subjects indicated that having XLA affected career choice a lot. There were few other areas that were commonly said to have been affected a lot by the diagnosis. Seven said that having XLA affected their lifestyle a lot. For all other areas, 5 or fewer subjects felt that XLA had had a major impact.

When asked how having XLA had affected their lives, the subjects commented frequently that their choice of jobs or careers was affected because they knew that they needed to have good insurance. Four subjects said that they had not been able to join the military because they had XLA. Several subjects noted that they had concerns about travel. Some said that they feared acquiring unusual infections; others said that scheduling the gammaglobulin therapy and travel was difficult. Thus, it was the treatment, rather than the signs and symptoms of the disease, that was burdensome to the subjects.

Discussion

The results of this study indicate that the majority of adult patients with XLA are doing surprisingly well. A high percentage of the patients less than 30 years old (76%) had not been hospitalized for infection since diagnosis; and, over 85% of all study subjects were working full time or were full time students. The quality of life in the adults with XLA was equivalent to that of otherwise healthy male adults; and, compared to the US population at large, the study subjects were less likely to be obese, less likely to smoke and less likely to have risky alcohol consumption. Less than a third of the adults with XLA indicated that they had chronic lung disease, and most of the individuals who reported chronic lung disease had minimal disability related to their disease.

Despite this optimistic overall assessment of the health status of the adults with XLA, most of the study subjects had some long-term medical problems that could be attributed to their disease. The majority had chronic or recurrent sinusitis, cough or bronchitis. Infections with unusual organisms, particularly mycoplasma and ureaplasma, may be responsible for arthritis, prostatitis and urethritis in some of the subjects [12,31]. Like other patients with immunodeficiency, patients with XLA are vulnerable to infection with organisms that are not pathogenic in otherwise healthy individuals [32]. These infections are often difficult to diagnose and difficult to treat.

Among the 10 individuals with XLA who died within the last 15 years, chronic liver disease and end stage pulmonary disease were equally important. In 3 of the 10 patients who died, hepatitis C infection, which may have been acquired through plasma therapy or contaminated intravenous gammaglobulin, played a major role. Because hepatitis C infection may remain asymptomatic for two or more decades [33], it is possible that additional patients with XLA will show signs of the disease in the future. However, plasma therapy is no longer used, and gammaglobulin preparations are now screened for hepatitis C virus, suggesting that the risk of hepatitis C in current and future patients is similar to that seen in otherwise healthy individuals.

One of the patients with XLA who died at greater than 21 years of age (Table 1) and one of the study subjects had neurologic damage due to enteroviral infection. In both cases, the enterovirus was acquired before the patient was treated with intravenous gammaglobulin. The absence of newly acquired enteroviral infections in the study subjects supports the hypothesis that adequate doses of gammaglobulin provide good protection against the severe consequences of enteroviral infection [34].

Our data do not provide a clear answer to the question of whether patients with XLA are at an increased risk of malignancy. Of the 87 adults with XLA who were potential subjects for this study, at least three have had cancer. One adult who could not be traced had a successfully treated colonic lymphoma at age 28. As noted in Table 1, one subject died of a rapidly progressive T cell lymphoma at 25 years of age. The third subject with cancer was the 57-year-old grandfather who had never received gammaglobulin therapy. This man reported two episodes of colonic cancer: one occurring at age 43 and the second at age 54. A variety of malignancies have been reported in patients with XLA including both T and B cell lymphomas [2,35], lung cancer [36] and a reticulum cell sarcoma of the bowel [2]. There have been several reports of gastrointestinal carcinoma in adults with XLA, both gastric carcinomas and carcinomas of the colon [37–40]. In the general population, gastrointestinal carcinomas are most commonly seen in people over 50 years of age, whereas the carcinomas seen in the patients with XLA have usually occurred at less than 50 years of age. Long-term infection or inflammation may predispose to malignancy in patients with XLA, but our study suggests that the risk is relatively small.

It is reasonable to ask if the study subjects were representative of all patients with XLA born before 1980. Most study subjects were recruited from families that had been referred for mutation detection. Families that are more sophisticated or who are receiving care at tertiary centers may be referred for genetic analysis more frequently than families at primary care centers. In addition, a high proportion of the study subjects had a prior family history of XLA; these patients were diagnosed at a younger age, and it is likely that they were treated more aggressively.

Furthermore, the adults included in this study may include a large proportion of patients with “milder XLA”. Both the subjects with and those without a positive prior family history

of XLA were older at the time of diagnosis than patients born during the same time period who were included in the analysis of XLA published by Lederman and Winkelstein in 1985 (3.1 years vs. 2.5 years for those with a positive family history of XLA and 5.8 years vs. 3.5 years for those without a family history of XLA) [2]. This observation supports the possibility that the study subjects were not as sick during their early childhood.

We have recently argued that the specific mutation in Btk may be one of the factors that contributes to disease severity [5,41]. As shown in Table 2, the study subjects had a statistically decreased proportion of frameshift mutations (5%), which are generally considered to be severe mutations; and, they had an increased proportion of splice site defects (34%), particularly defects occurring at base pairs that are conserved but not invariant in the consensus splice site. Splice site defects at conserved but not invariant sites are more likely to result in the production of a small amount of normal Btk transcript [27,42]. In the BTK base, a data base containing mutations from 823 families, identified using a variety of techniques, the proportion of frameshift mutations and splice defects was similar to that seen in our comparison group of 199 mutations (22% vs. 18% for frameshift mutations; and 16% vs. 18% for splice site defects) [6]. Thus, a milder mutation in Btk may be more likely to permit survival to adulthood.

Finally, the frequency of chronic lung disease in this study is based on a self-report. It may be that high resolution CT would reveal permanent changes in a higher percentage of subjects. Others have noted that chronic lung disease can develop in patients with XLA in the absence of any acute infections [4,9,43] and patients who slowly develop symptoms may not recognize them as being abnormal. There were some subjects who indicated that they coughed all of the time, but they did not report chronic lung disease. However, the number of subjects who indicated that they had dyspnea was small.

In the last 20 years, the outlook for patients with XLA has markedly improved. Patients are diagnosed at a younger age, and they are treated more aggressively and more effectively. As has been reported by others, patients with XLA who are treated with adequate doses of gammaglobulin are rarely hospitalized for acute, overwhelming infection [9]. However, these patients remain vulnerable to chronic low-grade infections. Collaborative studies will be required to evaluate strategies, like long-term prophylactic antibiotics, that might decrease the risk of these infections. Nevertheless, this study demonstrates that patients with XLA can function as relatively healthy productive adults.

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