X-Linked Agammaglobulinemia

Report on a United States Registry of 201 Patients

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Abstract: X-linked agammaglobulinemia (XLA) is a primary immunodeficiency caused by mutations in the gene for Bruton tyrosine kinase (BTK) that result in the deficient development of B lymphocytes and hypogammaglobulinemia. Because the disorder is uncommon, no single institution has had sufficient numbers of patients to develop a comprehensive clinical picture of the disorder. Accordingly, a national registry of United States residents with XLA was established in 1999 to provide an updated clinical view of the disorder in a large cohort of patients. A total of 201 patients were registered by 66 physicians. The estimated birth rate for the 10-year period of 1988–1997 was 1/379,000. Infection was the most common initial clinical presentation (85%), followed by a positive family history (41%) and neutropenia (11%). Although the average age of diagnosis was younger in patients with a positive family history (mean, 2.59 yr) than in patients with a negative family history (mean, 5.37 yr) ($p < 0.001$), only 34.5% of patients with a positive family history at the time of their birth were diagnosed before clinical symptoms developed—that is, based on family history alone. Seventy percent of patients had at least 1 episode of otitis, 62% at least 1 episode of pneumonia, 60% at least 1 episode of sinusitis, 23% at least 1 episode of chronic/recurrent diarrhea, 21% at least 1 episode of conjunctivitis, 18% at least 1 episode of pyoderma and/or cellulitis, 11% at least 1 episode of meningitis/encephalitis, 10% at least 1 episode of sepsis, 8% at least 1 episode of septic arthritis, 6% at least 1 episode of hepatitis, and 3% at least 1 episode of osteomyelitis. Fourteen of 201 (6.9%) patients were dead at the time they were entered in the Registry. However, in a prospective 4 ¼-year follow-up of living patients, only 3/80 (3.75%) patients died. Causes of death included disseminated enterovirus infection (n = 6), pulmonary insufficiency (n = 5), adenovirus infection (n = 1), sepsis (n = 1), acquired immunodeficiency disease syndrome (AIDS) (n = 1), myocarditis (n = 1), hepatitis (n = 2), and stem cell transplantation (n = 1).

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Abbreviations: BTK = Bruton tyrosine kinase, IVIG = intravenous immunoglobulin, XLA = X-linked agammaglobulinemia.

INTRODUCTION

X-linked agammaglobulinemia (XLA) is a primary immunodeficiency caused by mutations in the gene for Bruton tyrosine kinase (BTK) that result in the deficient development of B lymphocytes[6,11,14,38,39,41,50,53]. Affected individuals have hypogammaglobulinemia, markedly reduced levels of serum antibodies, and markedly reduced levels of B cells[6,11,14,38,39,40,41]. As a result, they have an increased susceptibility to a variety of encapsulated bacteria and enteroviruses, microorganisms for which antibody plays an especially critical role in host defense[12,14,25,30,35,38,39,41].

Since the description of the first patient by Bruton in 1952[6], a number of case reports have been published detailing many of the clinical characteristics of the disorder. However, because of the relative rarity of the disorder, it has been difficult for any single institution to develop a comprehensive picture of the disorder. A number of different series have been reported of patients with XLA[12,25,30,35,41,43]. One of these series was published 20 years ago and largely reflected earlier patterns of treatment, diagnosis, and practice in the United States in 96 patients[30]; another focused on the clinical findings leading to diagnosis in 82 patients[12]; another summarized infectious complications in 33 Iranian patients[35]; and yet another provided insight into the development of chronic lung disease in 73 Italian patients[41].

Accordingly, a national registry of United States residents with XLA was established in 1999 to provide an updated view of the disorder in a large cohort of patients, including a minimum estimate of the incidence of the disorder, characterization of some of its epidemiologic features, further delineation of its clinical features, and estimates of survival.

PATIENTS AND METHODS

Ascertainment of Patients

Patients were ascertained in 2 ways. First, in November 1996, all 17,000 members of 7 academic societies in the United States (American Academy of Allergy, Asthma and Immunology; Clinical Immunology Society; Society for Pediatric Research; American Society for Clinical

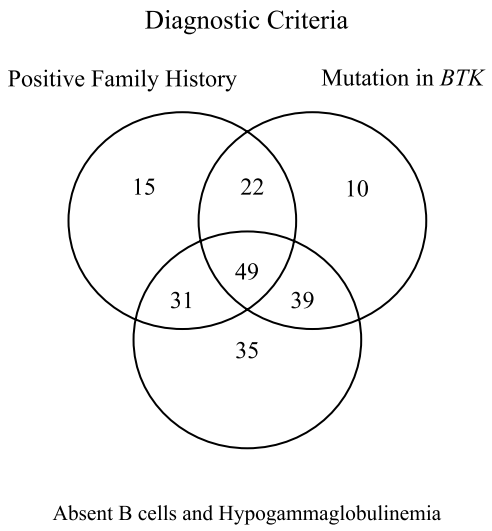

FIGURE 1. Diagnostic criteria of patients with X-linked agammaglobulinemia.

Investigation; American Pediatric Society; Infectious Diseases Society; and American Society of Hematologists) were sent a 1-page questionnaire inquiring if they had patients with XLA, or had had patients in the past, and if they would be willing to enter their patients in the Registry. Second, the chairpersons of all departments of pediatrics and internal medicine in the United States with residency training programs were sent the same questionnaire and requested to pass it on to the members of their faculties who might have patients with XLA.

The physicians who reported that they had patients with XLA were sent a 4-page Clinical Data Entry form in 1998 requesting detailed information on the demographic characteristics of the patient, the laboratory findings relating to the diagnosis of XLA, the clinical characteristics of the patient, and the patient's latest status. The first patient was registered in January 1999 and between then and December 2004, 201 patients were entered into the Registry.

In January 2004, a 1-page follow-up form was sent to each physician who had entered living patients in the Registry, requesting information as to the status of the patient at their last follow-up and when that follow-up had occurred. Follow-up information was available on 80 of the 148 patients (54%) who were alive when entered in the Registry before 2004; follow-up information was not obtained on the 53 patients entered into the Registry in 2004 after the follow-up survey had been initiated.

Construction of Registry

To maintain patient anonymity, the only identifying data collected were the patient's birth date, initials, sex, and race. The patient's name, address, phone number, social security number, and/or hospital number were not obtained. Duplicate entries from different physicians were avoided by cross-checking the patients' initials, birth dates, and race.

Diagnostic Criteria

Patients were considered to have XLA if they had 1) a mutation in the BTK gene and/or defective expression of the BTK protein, or 2) a positive family history of a maternally related lateral male relative with XLA (for example, either a mutation of the BTK gene or defective expression of the BTK protein or markedly reduced numbers of B lymphocytes in their blood [<2%] and hypogammaglobulinemia), or 3) markedly reduced numbers of B lymphocytes in their blood (<2%) and hypogammaglobulinemia. Of the 201 patients entered in the Registry, 120 (59%) were demonstrated to have a mutation in the gene for BTK, and/or defective expression of the BTK protein, 117 (58%) had a positive family history of a lateral male relative with XLA, and 154 (76%) had markedly reduced numbers of B cells (<2%) and hypogammaglobulinemia. Only 35 (17%) were diagnosed based exclusively on absent B cells and hypogammaglobulinemia. Most patients had more than 1 criterion for establishing the diagnosis (Figure 1), and all fulfilled established criteria for ''definitive'' or ''probable'' XLA[13].

RESULTS

Demographic Characteristics and Birth Rate

A total of 201 male patients from 122 unrelated families were registered by 66 physicians (see Acknowledgments). Of these, 161 were white, 13 were African-American, 2 were Asian, 2 were both white and Asian, and race was not reported in 23 patients.

The estimated minimal birth rate of XLA in the United States from 1988 through 1997 averaged 1 XLA patient/379,000 total births per year, or 1/190,000 male births per year based on total births in the United States (National Center for Health Statistics, Vital Statistics of the United States). The

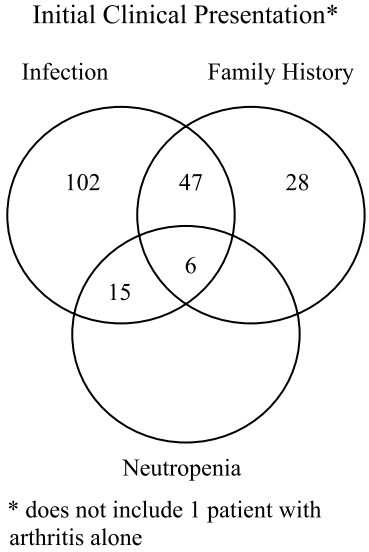

FIGURE 2. Initial clinical presentation of patients with X-linked agammaglobulinemia.

highest birth rate, 1/288,000 live births, was recorded in 1989. We used this 10-year period to estimate the birth rate of XLA in order to minimize the degree to which the incidence would be underestimated. For example, patients born decades before the Registry was established might have been more likely to have died before being diagnosed or might have been diagnosed but died before the physicians who participated in the Registry were at their current institutions. Similarly, patients born since 1997 might not yet have been diagnosed because of their young age (see below), and therefore would also be underrepresented in the Registry.

Initial Clinical Presentation

Information on the kinds of clinical problems that led to the initial diagnosis was available for 197 of the 201 patients (Figure 2). An increased susceptibility to infection was the most common initial clinical presentation, occurring in 170 patients (86%). A positive family history at the time of their birth led to the diagnosis in 81 patients (41%). However, only 28 of those 81 patients (34.5%) with a positive family history at the time of their birth were diagnosed solely on the basis of their positive family history, before any clinical symptoms had developed. Neutropenia was present in 21 patients (11%) at the time of their initial clinical presentation. No patient presented with isolated neutropenia; all patients with neutropenia as part of their initial clinical presentation also had an increased susceptibility to infection. The types of infections that preceded diagnosis included otitis media (n = 137; 69%), pneumonia (n = 106; 53%), sinusitis (n = 74; 37%), diarrhea (n = 27; 14%), conjunctivitis (n = 25; 13%), sepsis (n = 18; 9%), septic arthritis (n = 14; 7%), and cellulitis (n = 13; 7%). Two patients had vaccine-associated paralytic polio at the time of diagnosis, and 1 had a history of wild polio.

The age at which the increased susceptibility to infection became apparent in those patients who developed clinical symptoms before diagnosis is displayed in Figure 3. Over 50% of the symptomatic patients presented clinically by 1 year of age, with nearly all patients symptomatic by age 5; only 3 patients were reported to have developed symptoms after age 5 years.

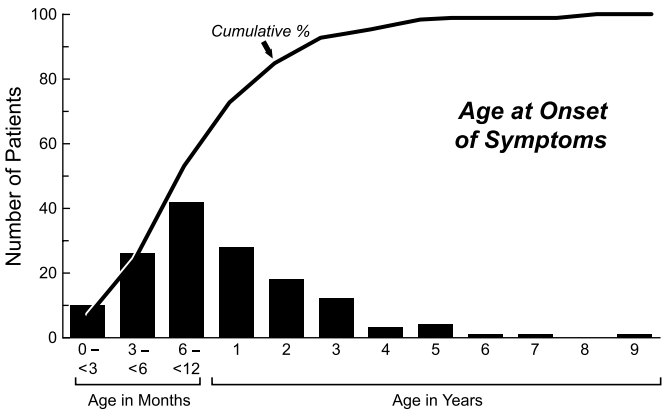

FIGURE 3. Age at onset of symptoms of patients with X-linked agammaglobulinemia.

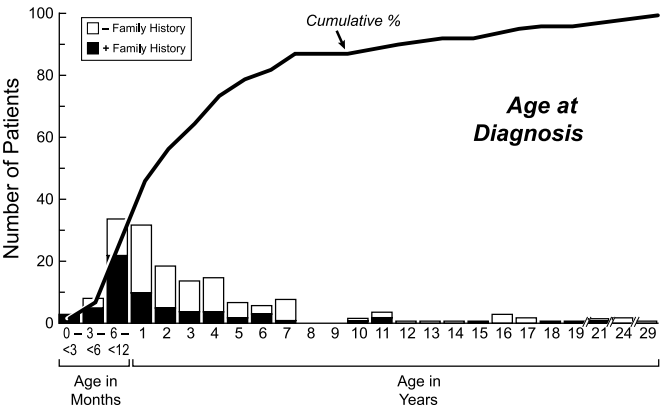

FIGURE 4. Age at diagnosis of immunodeficiency of patients with X-linked agammaglobulinemia.

Age at Diagnosis

The age at diagnosis was reported for 175 patients. Fifty percent of patients were diagnosed with agammaglobulinemia/hypogammaglobulinemia by age 2 years (Figure 4), although a specific diagnosis of XLA may have followed in some patients years later. The patients with a positive family history at the time of their birth were diagnosed significantly earlier (mean, 2.59 yr) than those without a family history (mean, 5.37 yr) ($p < 0.001$), although only 34.5% of those with a positive family history at the time of their birth were diagnosed before they developed clinical symptoms referable to their immunodeficiency. There was an inverse relationship between the patient's year of birth and age of diagnosis (Pearson correlation; $R = -.43$; $p < 0.0001$); the patients born earlier were diagnosed later in life. However, since some patients were born before the first description of the disease in 1952, we also analyzed this relationship in the

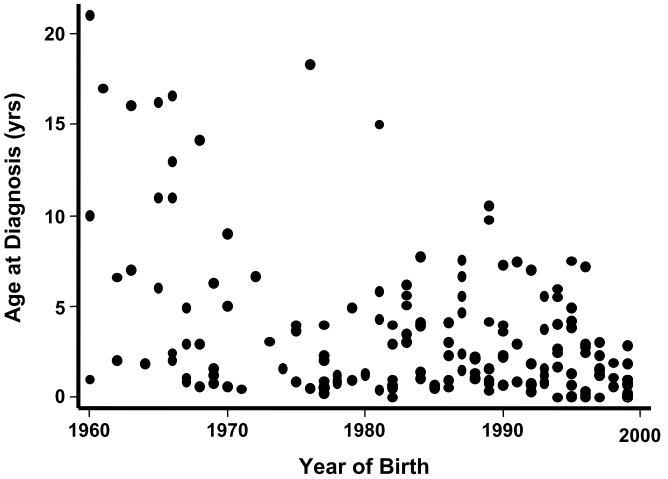

FIGURE 5. Relationship between year of birth and age at diagnosis of immunodeficiency.

subset of patients born after 1960, and the inverse relationship held true for them as well ($R = -.31$; $p < 0.0001$) (Figure 5).

Immunoglobulin Levels at Diagnosis

The levels of serum immunoglobulins at the time of the initial diagnosis of hypogammaglobulinemia, before the institution of gamma globulin therapy, are displayed in Figure 6. All but 3 patients had reduced levels of IgG. Two of those 3 patients had IgG levels just above the lower limit of normal when they were less than 3 months of age, a point in time when their IgG level probably still reflected some of the IgG actively transplacentally transferred from their mother. The remaining patient had an IgG level of just over 400 mg/dL at 10 months of age, a point in time when little maternally transferred IgG would be present; it should be noted that this patient had a mutation in the BTK gene. Although the overwhelming majority of patients had reduced levels of IgA and IgM, 11 patients had normal levels of IgA

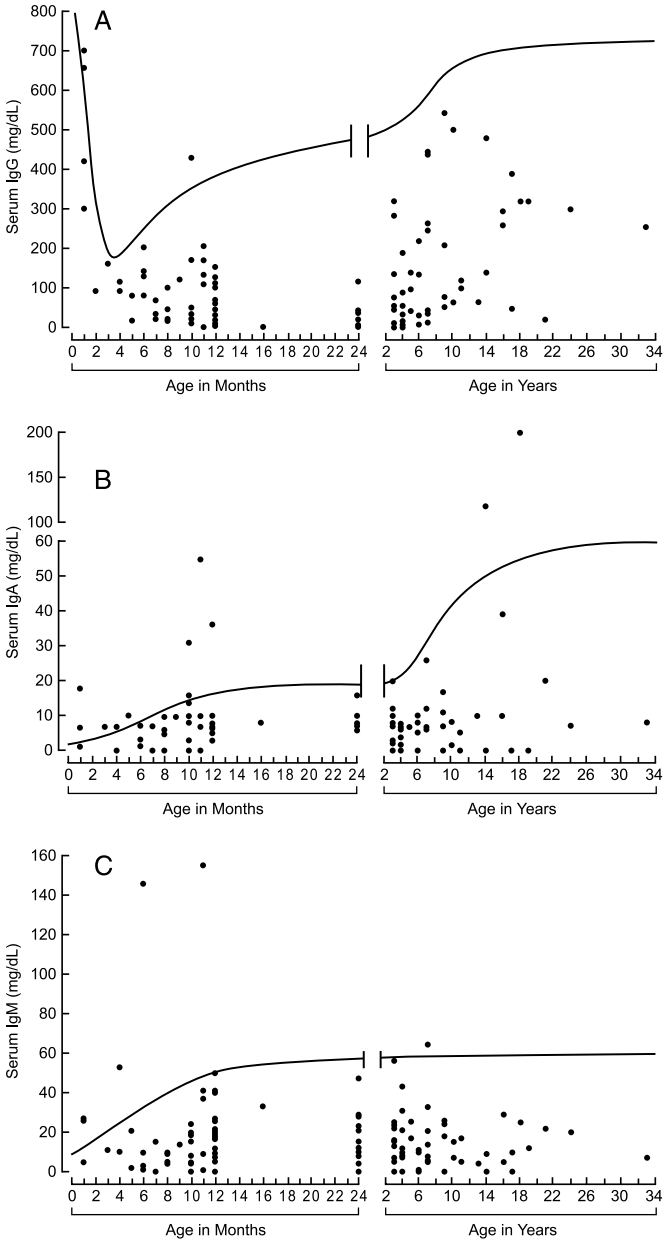

FIGURE 6. Immunoglobulin levels at time of diagnosis of immunodeficiency in patients with X-linked agammaglobulinemia. The solid lines represent the lower limits of normal.

TABLE 1. Prevalence of Infections

Infection	No. of Patients (%)* (n = 201)
Upper respiratory	
Otitis	140 (70)
Sinusitis	119 (59)
Mastoiditis	1
Pneumonia	125 (62)
Chronic/recurrent diarrhea	46 (23)
Conjunctivitis	42 (21)
Pyoderma/cellulitis/subcutaneous abscess	36 (18)
7Meningitis/encephalitis	25 (12)
Sepsis	21 (10)
Septic arthritis	15 (7)
Hepatitis	13 (6)
Osteomyelitis	6 (3)
Miscellaneous	
Vaccine-related polio	2
Wild polio	1
Hand-foot-and-mouth disease	1

*Number (and percentage) of patients who had at least 1 episode of the given infection. The percentages add up to more than 100% because some patients had more than 1 type of infection.

TABLE 2. Etiology of Pneumonia

Organism	No. of Patients (%)* (n = 125)
Pneumococcus	9 (7)
H. influenzae, type b	5 (4)
Pseudomonas spp	3 (2)
Staphylococcus spp	3 (2)
H. parainfluenzae	3 (2)
H. parahemolytica	1 (1)
Klebsiella spp	1 (1)
Mycobacterium avium	1 (1)
Pneumocystic carinii	1 (1)
Measles	1 (1)
Unknown/not reported	105 (84)†

*Number (and percentage) of patients who had at least 1 episode of pneumonia caused by the specific organism. The percentages add up to more than 100% because some patients had more than 1 episode of pneumonia.

†Number (and percentage) of patients who had 1 or more episodes of pneumonia but never had an etiologic agent identified.

TABLE 3. Etiology of Chronic/Recurrent Diarrhea

Organism	No. of Patients (%)* (n = 46)
Giardia lamblia	12 (26)
Rotavirus	4 (9)
Campylobacter fetus	3 (7)
Enterovirus	3 (7)
Salmonella spp	3 (7)
C. difficile	2 (4)
Helicobacter pylori	1 (2)
Shigella spp	1 (2)
Unknown/not reported	21 (45)†

*Number (and percentage) of patients who had at least 1 episode of diarrhea caused by the specific organism. The percentages add up to more than 100% because some patients had more than 1 episode of diarrhea.

†Number (and percentage) of patients who had 1 or more episodes of diarrhea but never had an etiologic agent identified.

and 5 patients had normal levels of IgM. Of the 5 patients with normal IgM levels, 4 had documented mutations in BTK and the fifth had less than 1% B cells and a lateral male relative with XLA.

Prevalence of Infections

The most common infection was otitis media, occurring in 70% of patients (Table 1). Pneumonia was also common, occurring in 62% of patients, followed by sinusitis (59%), chronic and/or recurrent diarrhea (23%), conjunctivitis (21%), infections of the skin and subcutaneous tissue (18%), meningitis/encephalitis (11%), sepsis (10%), septic arthritis (7%), hepatitis (6%), and osteomyelitis (3%). Two patients were reported to have had vaccine-associated paralytic polio, while 1 survived wild polio.

Etiology of Infections

The most common etiologies of some of the different infections are displayed in Tables 2–6.

TABLE 4. Etiology of Meningitis/Encephalitis

Organism	No. of Patients (%)* (n = 25)
S. pneumoniae	5 (20)
ECHOvirus	4 (16)
Coxsackievirus	2 (8)
Poliovirus	3 (12)†
Adenovirus	1 (4)
H. influenzae, type b	1 (4)
Unknown/not reported	9 (36)‡

*Number (and percentage) of patients who had at least 1 episode of meningitis/encephalitis caused by the specific organism.

†Two cases of vaccine-associated paralytic polio and 1 of wild polio.

‡Number (and percentage) of patients who had 1 or more episodes of meningitis/encephalitis but never had an etiologic agent identified.

TABLE 5. Etiology of Sepsis

Organism	No. of Patients (%)* (n = 21)
Pseudomonas spp	6 (29)
S. pneumoniae	5 (24)
H. influenzae, type b	1 (5)
Campylobacter fetus	1 (5)
Helicobacter cinaidi	1 (5)
Salmonella spp	1 (5)
Unknown/not reported	6 (29)†

*Number (and percentage) of patients who had at least 1 episode of sepsis caused by the specific organism.

†Number (and percentage) of patients who had 1 or more episodes of sepsis but never had an etiologic agent identified.

Pneumonia

The majority of patients (84%) with pneumonia did not have an etiologic agent identified (Table 2). The pneumococcus was the most common organism among those patients in whom an etiologic agent was isolated, followed by *Haemophilus influenzae*, type b; *Haemophilus parainfluenzae*; *Pseudomonas* species; and *Staphylococcus* species. One patient with a mutation in the BTK gene did have documented *Pneumocystis carinii* pneumonia, another patient with a mutation in the BTK gene had *Mycobacterium avium* pneumonia, and a third patient with absent B cells and a positive family history of a lateral male relative with XLA had measles pneumonia after exposure to the wildtype virus.

Chronic and/or Recurrent Diarrhea

Over half of the patients with chronic and/or recurrent diarrhea had an organism identified. *Giardia lamblia* was the most common organism isolated, followed by rotavirus, *Campylobacter fetus*, enterovirus, and *Salmonella* species (Table 3).

Meningitis and Encephalitis

The most common causes of a central nervous infection were enteroviruses (Table 4), specifically ECHOvirus, Coxsackievirus, and poliovirus, all of which presented as encephalitis. The pneumococcus species was the most

TABLE 6. Etiology of Hepatitis

Organism	No. of Patients (%)* (n = 13)
Hepatitis C	8 (62)†
Unknown/not reported	5 (38)‡

*Number (and percentage) of patients who had at least 1 episode of hepatitis caused by the specific organism.

†Four of these reportedly due to IVIG.

‡Number (and percentage) of patients who had 1 or more episodes of hepatitis but never had an etiologic agent identified.

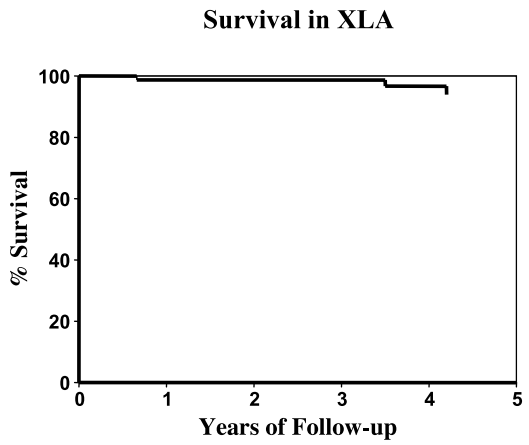

FIGURE 7. Kaplan-Meier plot of survival of patients with X-linked agammaglobulinemia.

common cause of bacterial central nervous infection, all cases of which were meningitis.

Sepsis

Pseudomonas species were the most common organisms isolated in patients with sepsis (Table 5) followed by *Streptococcus pneumoniae*. Individual patients also had *Haemophilus influenzae*, type b; *Campylobacter fetus*; *Helicobacter cinaidi*; and *Salmonella* species.

Hepatitis

Eight of 13 patients with hepatitis were reported to have hepatitis C (Table 6); in 4 of these 8 patients, contaminated intravenous immunoglobulin (IVIG) was considered to be the source.

Osteomyelitis and Septic Arthritis

Too few patients had organisms reported to provide meaningful data on osteomyelitis and septic arthritis.

Malignancies

Four patients were reported to have malignancies. One each with osteosarcoma, lymphoma, and reticulum cell sarcoma had had the malignancy diagnosed by the time they were entered in the Registry. An additional patient developed adenocarcinoma of the colon after having been entered in the Registry.

Miscellaneous Clinical Findings

Neutropenia occurred in 21 patients but only at the time of diagnosis. Two patients developed membranoproliferative glomerulonephritis. Four patients developed unexplained central nervous system deterioration; in none was an enterovirus isolated from meningeal fluid, stool, or oral mucosa.

Outcome

Of the 187 patients who were alive at the time they were entered in the Registry, 48 (26%) were 21 years of age or older.

A total of 17 of the 201 patients (8.5%) in the Registry died. Fourteen of the 201 patients (6.9%) had died at the time they were entered in the Registry. Follow-up information was available on 80 of the 148 patients (54%) who had been entered in the Registry before 2004 when the follow-up survey was performed. Of these 80, an additional 3 patients died (3.75%) during the period of follow-up (Figure 7).

The causes of death of the 17 patients who died are listed in Table 7. Six of the 17 (35%) died of disseminated

TABLE 7. Cause of Death

Year of Birth	Age at Death (yr)	Cause of Death	Status at Entry into Registry
1947	50	Disseminated ECHOvirus; chronic lung disease	Dead
1950	29	Hepatitis; non-A, non-B	Dead
1960	27	AIDS	Dead
1960	36	Adenovirus encephalitis	Dead
1961	35	Chronic lung disease	Dead
1963	26	Chronic lung disease	Dead
1964	16	Chronic lung disease	Dead
1964	40	Hepatitis C from IVIG	Alive
1967	9	Disseminated ECHOvirus	Dead
1969	6	Disseminated ECHOvirus	Dead
1975	25	Disseminated ECHOvirus	Dead
1978	26	Renal failure and sepsis	Alive
1981	6	Disseminated Coxsackievirus	Dead
1986	13	Chronic lung disease	Dead
1988	8	Disseminated ECHOvirus	Dead
1997	3	Myocarditis	Dead
1998	6	Complications of stem cell transplantation	Alive

enteroviral infections, 4 (25%) died of chronic lung disease, and 2 (15%) died of hepatitis. Of the 3 patients who died after being entered in the Registry, 1 died of hepatitis C contracted from IVIG, 1 died of renal failure and sepsis secondary to membranoproliferative glomerulonephritis, and 1 died following an attempt at stem cell transplantation.

Finally, we compared the outcomes of patients in whom XLA was documented by mutational analysis with those who were not examined for a mutation. There was no difference between the 2 groups in any outcome, including death rate or prevalence of vaccine-associated polio, systemic enteroviral infections, meningitis, encephalitis, pneumonia or sepsis.

DISCUSSION

Because XLA is uncommon, most early reports described limited clinical and/or laboratory features in small numbers of patients. There have been, however, 4 clinical series of patients with XLA: 1 of 96 patients in the United States published in 1985[30], another of 44 patients in the United Kingdom published in 1993[25], another of 73 patients in Italy published in 2002[41], and another of 33 patients in Iran published in 2004[35]. These clinical series provided a broader insight into the clinical features of the disorder, but the first 2 were limited by the fact that molecular genetic validation of the diagnosis was not possible when they were published.

The current series reflects the findings of a national registry of over 200 United States residents with XLA. As such it provides the opportunity to estimate the minimum birth rate of the disorder, characterize some of the demographic features in the United States, describe the initial clinical features leading to diagnosis, define the clinical characteristics, and provide insight into the outcome of the disorder in a large cohort of patients.

Incidence of XLA

It has been difficult to establish accurate estimates of the incidence or prevalence of most of the primary immunodeficiency diseases. In 1 instance, C2 deficiency, a single mutation accounts for over 95% of all patients. Therefore screening populations for C2 heterozygotes by PCR has been possible, and the frequency of homozygous deficient individuals in the population has been calculated[49]. In another instance, selective IgA deficiency, the disorder occurs commonly enough to allow screening of selected populations and detection of affected individuals directly[2,9,20,22,27,37]. However, for most of the primary immunodeficiency diseases there is not a single mutation responsible for the deficiency, nor do they occur commonly enough to allow for population screening at the present time.

Registries of primary immunodeficiency diseases have been established in a number of countries[5,19,32,33,44,48,57], but in most instances, any given primary immunodeficiency, such as XLA, has been reported as a percentage of the total number of patients with primary immunodeficiency rather than as birth rates. Thus, patients with XLA have been reported to constitute from 6% to 11% of patients with primary immunodeficiency diseases[5,19,32,33,44,48,57]. However, 3 national registries have reported an incidence or birth rate for XLA: in Switzerland the birth rate was estimated as 1/200,000 live births[44], in Spain the birth rate was estimated at between 1/10,000,000 and 1/20,000,000 live births[33], and in Norway the birth rate was estimated at between 1/100,000 and 1/285,000 live births[48].

Birth rate data obtained from the Registry suggest that the minimum birth rate for XLA in the United States is approximately 1/379,000 live births for the 10 years between 1988 and 1997. The highest birth rate was in 1989 and was 1/288,000. This figure is most certainly an underestimate since not all physicians in the United States were contacted, not all physicians who were contacted participated, and not all patients may have been diagnosed or had adequate laboratory evaluation to qualify for entry into the Registry.

Initial Clinical Presentation and Diagnosis

Over half of the patients developed symptoms referable to their immunodeficiency before 1 year of age, and more than 90% by 5 years of age. Fewer than 10% had symptoms in the first 3 months of life, an observation consistent with the fact that they were protected by the transplacental transfer of maternal antibody. An increased susceptibility to infection was the exclusive clinical symptom that brought patients to attention. In approximately 15% there was concurrent neutropenia. Otitis media was the most common infection preceding diagnosis, with pneumonia, sinusitis, diarrhea, conjunctivitis, sepsis, septic arthritis, and cellulitis each occurring in a significant number of patients before diagnosis. In a previous study focusing on clinical findings leading to the diagnosis of XLA, otitis was also the most common infection[12]. As has been pointed out by others, the occurrence of an increased susceptibility to infection and absence of tonsils should alert physicians to the possibility of XLA[12], even in the absence of a positive family history. Similarly, XLA should be included in the differential diagnosis of the child with an increased susceptibility to infection and neutropenia[7,10,18,26,42].

Over half of the patients were diagnosed with agammaglobulinemia/hypogammaglobulinemia by 2 years of age, with nearly 80% diagnosed by school age. However, a few patients were not diagnosed until adolescence or adulthood, some in spite of a positive family history at the time of their birth. Other authors have reported families in which affected individuals have not been diagnosed with an immunodeficiency until adulthood, some of whom had relatively mild symptoms and/or late onset of symptoms[8,24,28,36,45,47,51].

Eighty-one patients were born into a family with a previously affected family member, either a brother, maternal cousin, or maternal uncle. Unfortunately, only 28 of those 81 patients (34%) were diagnosed based on their family history alone, before developing any clinical symptoms. In an earlier study on XLA published in 1985, only 12% of patients with a positive family history reported at the time of their

diagnosis were diagnosed before developing clinical symptoms[30]. We hope that the current figure of 34% represents a trend over the last 2 decades toward improvement in using a positive family history as an aid to presymptomatic diagnosis. Nevertheless, it does indicate that the presence of a positive family history did not contribute as often as it could have to an early diagnosis in presymptomatic children. A previous study[56] on another X-linked primary immunodeficiency, the X-linked Hyper-IgM syndrome, gave similar results, with only 33% of patients with a positive family history at the time of their birth being diagnosed before clinical symptoms developed.

Analysis of the patient's year of birth and age at diagnosis revealed that patients born more recently were diagnosed at an earlier age than those born earlier. In fact, only 1 patient born in the last 25 years was diagnosed at an age older than 10 years. With more awareness of the clinical presentation of this uncommon primary immunodeficiency and more attention to family history, we hope that even earlier diagnosis and therapy can be accomplished. This is especially important, since early diagnosis and therapy with intravenous gammaglobulin have been shown to improve outcome in patients with XLA[41,43].

Infections

The most common infections, both before and after diagnosis and treatment, were upper respiratory infections, such as otitis media and sinusitis, pneumonia; chronic/recurrent diarrhea; conjunctivitis; and skin infections. Although blood-borne infections such as sepsis, meningitis/encephalitis, septic arthritis, and osteomyelitis also occurred, they were much less common. The specific etiologic agent was usually not reported for respiratory infections, such as otitis, sinusitis, or pneumonia. However, for the other infections, the etiologic agents were often identified. The most common for each included *Giardia* for diarrhea, *Streptococcus pneumoniae* for meningitis, *Pseudomonas* for sepsis, and hepatitis C virus for hepatitis. Notably, at least half of the cases of hepatitis C were the result of contaminated IVIG.

Although the majority of infections were caused by common encapsulated bacteria, there are some infections that deserve special attention. Enteroviral infections, such as Coxsackievirus and ECHOvirus, have been especially difficult infections in patients with XLA[4,23,34,39,55]. The infections are usually chronic and systemic in nature. Their primary clinical manifestation is encephalitis/meningitis, although hepatitis, pneumonia, and dermatomyositis have also been seen. Six of the patients in the current series had systemic enteroviral infections, all of whom died. It is important to note that all but 1 of the patients developed the systemic enteroviral infection before diagnosis and therapy, and the 1 patient who developed the infection after diagnosis had been treated only with intramuscular gammaglobulin. None of the patients in the current series treated with IVIG developed a systemic enteroviral infection while on therapy, although others have described isolated cases of enteroviral infections occurring in patients on IVIG therapy[23,34].

Two patients developed vaccine-related poliomyelitis but they both contracted the infection before diagnosis. It is noteworthy that another patient in the Registry contracted what was thought to be wild polio in 1948 and survived; he currently has postpolio syndrome[45].

Pneumocystis carinii pneumonia was seen in 1 patient in the current Registry with molecular genetic validation of the XLA diagnosis[46]. Males with congenital hypogammaglobulinemia have previously been described with *Pneumocystis carinii* pneumonia[1,15,39,46], and at least 3 of these have had mutational analysis documenting XLA[1,15,46]. We note that the patient in the current series and 1 of the other patients in the literature were noted to have poor nutritional status at the time of the *Pneumocystis carinii* pneumonia, a known risk factor. Thus, although it occurs infrequently, *Pneumocystis carinii* pneumonia can be seen in patients with XLA. In this regard, it is interesting that although T cells play a critical role in host defense against *Pneumocystis carinii*, B cells and opsonizing antibody have been shown to participate in host defense against *Pneumocystis carinii* pneumonia infection[17,31,54].

Malignancies

A variety of malignancies have been described in patients with XLA[3,16,21,29,30,52]. Four patients in the current series developed malignancies; 3 patients had lymphoreticular malignancies and 1 had colon cancer. In 1 report, colorectal cancer was found in 3 patients in a series of 52 patients (6%)[52]. It is notable that in 1 series of 73 patients with XLA[41] and in another of 44 patients with XLA[25], no malignancies were found. Until formal epidemiologic studies are performed, it will be difficult to determine which tumors patients with XLA are susceptible to, and what their degree of risk is.

Outcome

In the current series, 17 of 201 patients (8.5%) died; 14 before being entered in the Registry and another 3 during a $4^1/_4$-year follow-up. The most common cause of death was a chronic enteroviral infection, followed by chronic lung disease and hepatitis. It should be noted that the overwhelming majority of patients who died of chronic enteroviral infections contracted the infection before diagnosis and institution of immunoglobulin therapy. Similarly, most of the patients who died of chronic lung disease were diagnosed in an era when early diagnosis was not common, and well before adequate doses of gammaglobulin could be delivered to patients. Thus, the deaths of many of the patients might have been prevented with earlier diagnosis and more adequate therapy, both of which reflect today's situation.

Estimating survival in XLA using those patients who were dead at the time of registration is subject to a number of limitations. For example, physicians currently at an institution may not be aware of patients who died before that physician was at the institution, thereby underestimating deaths. Conversely, in some instances patients who died while a reporting physician was caring for them may have

been reported, but some living patients whose care was no longer at the institution may have been underreported, thereby overestimating deaths. Accordingly, we attempted to obtain survival data prospectively on a cohort of living patients. During the $4^1/_4$-year follow-up, 3 of those 80 patients died, yielding a death rate of approximately 1%/yr. It should be noted, however, that 2 of those 3 patients died of iatrogenic causes: 1 from hepatitis C contracted from IVIG contaminated with hepatitis C virus, and another following a stem cell transplantation. Thus, the prognosis of XLA, if diagnosed and treated before long-term complications of infection occur, appears to be excellent.

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