X-linked agammaglobulinemia (XLA): Phenotype, diagnosis, and therapeutic challenges around the world


*Corresponding author. Division of Allergy and Immunology, Wallace Chair of Pediatrics, Immunology Clinic, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104-4399, USA.

E-mail addresses: zeinabawad@gmail.com (Z.A. El-Sayed), jucapul_84@hotmail.com (J.C. Aldave), weenh@hotmail.com (W. Al-Herz), lbezrodnik@yahoo.com.ar (L. Bezrodni), rachida_boukari@yahoo.fr (R. Boukari), profbousfiha@gmail.com (A.A. Bousfiha), caterina.cancrini@opbg.net (C. Cancrini), antoniocondino@gmail.com (A. Condino-Neto), gdibaibo@aub.edu.lb (G. Dhaibo), beata.derfalvi@iwk.minsaith.ca (B. Derfalvi), efdogu@yahoo.com (F. Dogu), david.edgar@belfasttrust.hscni.net (J.David M. Edgar), Brian.Eley@uct.ac.za (B. Eley), rashahasan@med.asu.edu (R.H. El-Owaydi), saralaevespino@gmail.com (S.E. Espinosa-Padilla), nermeenagal@gmail.com (N. Galal), filomeen.haerynck@Ugent.be (F. Haerynck), rh08@aub.edu.lb (R. Hanna-Wakim), elham.hosnay@gmail.com (E. Hosnay), aydani@medicince.ankara.edu.tr (A. Ikinciogullari), dr.ebtihal.kamal.al@gmail.com (E. Kamal), hkanegane.ped@tmd.ac.jp (H. Kanegane), lauyung@hku.hk (Y.L. Lau), tmorio.ped@tmd.ac.jp (T. Morio), moschese@med.uniroma2.it (V. Moschese), joao.farelaneneves@chic.min-saude.pt (J.F. Neves), moniahasan@yahoo.fr (M. Ouedernia), robertopaganelli@unicht.it (R. Paganelli), kparis@lubhsc.edu (K. Paris), claudio.pignata@unina.it (C. Pignata), plebani@med.unibs.it (A. Plebani), farah.qamar@aku.edu (F.N. Qamar), sonia.queresi@aku.edu (S. Qureshi), nitaradhakrishnan@yahoo.com (N. Radhakrishnan), rezaei.nima@yahoo.com (N. Rezaei), nelson.rosario@onda.com.br (N. Rosario), jrouites@mcm.edu (J. Routes), bersanchez@yahooy.es (B. Sanchez), Anna.Sediva@fnmotol.cz (A. Sediva), milko.seppanen@hus.fi (M.R.J. Seppanen), negrette@gmail.com (E.G. Serrano), shcher26@hotmail.com (A. Shcherbina), surjitsinghp@rediffmail.com (S. Singh), sang.8@yahoo.com (S. Siniah), giuseppe.spadaro@uniroma1.it (G. Spadaro), Mimi.Tang@rch.org.au (M. Tang), anavire@gmail.com (A.M. Vinet), volokha@gmail.com (A. Volokha), sullivank@email.chop.edu (K.E. Sullivan).

Abbreviations: CLD, Chronic lung disease; FH, Family history; GI, Gastrointestinal; JIA, juvenile idiopathic arthritis; SCIG, Subcutaneous immunoglobulin; VAPP, Vaccine associated paralytic poliomyelitis; XLA, X-linked agammaglobulinemia.

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Background: X-linked agammaglobulinemia is an inherited immunodeficiency recognized since 1952. In spite of seven decades of experience, there is still a limited understanding of regional differences in presentation and complications. This study was designed by the Primary Immunodeficiencies Committee of the World Allergy Organization to better understand regional needs, challenges and unique patient features.

Methods: A survey instrument was designed by the Primary Immunodeficiencies Committee of the World Allergy Organization to collect both structured and semi-structured data on X-linked agammaglobulinemia. The survey was sent to 54 centers around the world chosen on the basis of World Allergy Organization participation and/or registration in the European Society for Immunodeficiencies. There were 40 centers that responded, comprising 32 countries.

Results: This study reports on 783 patients from 40 centers around the world. Problems with diagnosis are highlighted by the reported delays in diagnosis—24 months in 34% of patients and the lack of genetic studies in 39% of centers. Two infections exhibited regional variation. Vaccine-associated paralytic poliomyelitis was seen only in countries with live polio vaccination and two centers reported mycobacteria. High rates of morbidity were reported. Acute and chronic lung diseases accounted for 41% of the deaths. Unusual complications such as inflammatory bowel disease and large granular lymphocyte disease, among others were specifically enumerated, and while individually uncommon, they were collectively seen in 20.3% of patients. These data suggest that a broad range of both inflammatory and autoimmune conditions can occur in patients. The breadth of complications and lack of data on management subsequently appeared as a significant challenge reported by centers. Survival above 20 years of age was lowest in Africa (22%) and reached above 70% in Australia, Europe and the Americas. Centers were asked to report their challenges and responses (n = 116) emphasized the difficulties in access to immunoglobulin products (16%) and reflected the ongoing need for education of both patients and referring physicians.

Conclusions: This is the largest study of patients with X-linked agammaglobulinemia and emphasizes the continued morbidity and mortality of XLA despite progress in diagnosis and treatment. It presents a world view of the successes and challenges for patients and physicians alike. A pivotal finding is the need for education of physicians regarding typical symptoms suggesting a possible diagnosis of X-linked agammaglobulinemia and sharing of best practices for the less common complications.

Introduction

XLA, a primary immunodeficiency disorder (XLA OMIM 300755), was first described in 1952 as a congenital agammaglobulinemia. As one of the first recognized inborn errors of immunity, it represents a primary immunodeficiency with significant data on outcomes and clinical features. The gene affected in XLA, Bruton tyrosine kinase (BTK), was discovered by two independent groups and is located on X-chromosome (Xq21.3—
Xq22.1,2 The critical role of BTK in B cell development is evident by the universal B cell deficiency (<2%) and absent precursor B cell differentiation in the bone marrow in patients with pathogenic mutations. Lymphocytes in their blood and tissues fail to generate plasma cells and have severely decreased production of all classes of immunoglobulins with markedly defective antibody responses. B-lineage cells in all organs are affected resulting in reduced sizes of lymph nodes and tonsils.

The genetic understanding is mature and XLA has been identified as the most common cause of agammaglobulinemia. Approximately 85% of patients with early onset of infections, panhypogammaglobulinemia, and less than 2% CD19+ B cells in the peripheral circulation have XLA.3,4 Autosomal recessive agammaglobulinemia has been associated with mutations in several other genes such as the μ heavy chain gene (IGHM MIM 601495), J5 (IGLL1 MIM 146770), ιγ (CD79A MIM 112205), Igβ (CD79B MIM 147245), BLNK (BLNK MIM 613502), PIK3R1 (PIK3R1 MIM 615214), and TCF3 (TCF3 MIM 616941).9,10 Autosomal dominant agammaglobulinemia was reported as a result of mutations in the LRRC8A gene on chromosome 9q34 and TCF3 gene on 19p13.3.11,12 The estimated incidence of XLA ranges from 1:100,000 to 1:200,000 live births.13-17

Early reports of patients with XLA focused on infection as the most common presenting manifestation of XLA.18 Nevertheless, it is not clear if the specific infections vary from country to country or region to region. In a report from Seoul, Korea, recurrent infections observed included pneumonia, acute otitis media, septic arthritis, skin infection, sepsis, sinusitis, acute gastroenteritis, cervical lymphadenitis, epididymitis, meningitis, osteomyelitis, urinary tract infection and encephalitis. One patient died of hematopoietic carcinoma secondary to hepatitis B virus, an infection not often reported in North America.19 In Africa, diarrhea was more common than in European cohorts with nearly half of the patients with chronic diarrhea.8 Less frequently reported complications of XLA include neutropenia, usually with Pseudomonas infection at the time of diagnosis, and the devastating enteroviral meningocencephalitis.20,21 Some manifestations may be associated with delay in diagnosis, however, differences in infection pattern may also be related to regional variation in exposure.22 A goal of this study was to identify regional differences in the infection pattern.

With the use of both a patient survey and USIDNET Registry data, 4% of XLA patients were found to have been diagnosed with Crohn’s disease in the USA.23 Arthritis occurred in 16%, a less frequent feature in Italy where it was seen in just 10%24 but seen in 29% of XLA patients reported from China.25 Collectively, the burden of comorbidities impact the quality of life of patients.20 These country or region-specific reports suggest that there may be differences in the clinical features of XLA around the world.

XLA patients are treated with replacement immunoglobulin and prophylactic antibiotics to prevent infections.26 Immunoglobulin may be administered either intravenously (IVIG) or subcutaneously (SCIG) at intervals of 2–4 weeks for the intravenous route and 1–14 days for the subcutaneous route. Recently, a new formulation for the administration of SCIG, using recombinant human hyaluronidase to facilitate the subcutaneous route. The adequacy of IgG replacement is determined by the administration of large volumes of SCIG on a monthly basis has been of SCIG, using recombinant human hyaluronidase to facilitate the

Characteristics of reporting centers

Data were collected from 40 centers representing 32 countries (Table 1). We asked three questions to understand the care delivery model across the countries: insurance/health coverage, the age of the center and how many living XLA patients are followed at each center. Healthcare coverage was largely skewed towards government coverage: 54% of centers reported comprehensive coverage, 27% reported some government coverage, 7% reported private insurance and 7% reported self-pay. As expected, there was heterogeneity in size and age of the centers, although 90% of the centers have been following patients for over ten years, supporting the concept that immunodeficiency is a maturing specialty (Table 2). These descriptive data provide a landscape for understanding healthcare as it relates to the care of patients with XLA.
Diagnosis and management options

Four questions established the mode of diagnosis at each center and the treatments most frequently utilized (Table 3). All centers used flow...
cytometry for diagnosis but genetic testing was widely utilized as well (in 61% of centers). The lag from the time of first complaint to diagnosis varied widely with 34% of centers reporting delays of more than 24 months. The delay was not related to type of health insurance coverage (ANOVA analysis not significant). Nearly all centers (98%) utilized immunoglobulin replacement as their main treatment, however access to subcutaneous immunoglobulin (SCIG) was reported by only 61% of centers.

Survival

Most centers (78%) reported that patients with XLA had a good survival rate with an average life span of over 15 years of age, however, only 62% of centers who saw adults reported that >75% of their patients with XLA survived beyond 20 years of age. The causes of death were highly varied. Eleven centers reported no deaths. There were 46 causes of death reported. Among the listed causes, chronic lung disease or acute lung disease were the most common 19/46 (41%). Sepsis was listed for six deaths (13%). There were six deaths from CNS infection/enterovirus (13%). Two patients had colitis listed as a cause of death. The remainder of the distinct causes were listed only once (cachexia with concomitant TIMM8A deletion, aneurysm, stomach cancer, hepatitis C, among others). When we assessed regional effects on survival, there were clear differences by continent (Table 4).

Unusual complications

This large cohort of patients with XLA allowed us to define the frequencies of complications previously reported in small series or case reports and to explore whether there is regional variation (inflammatory bowel disease, entero viral disease, large granular lymphocyte disease, arthritis, chronic cutaneous ulcers (usually due to Campylobacter) and vaccine-associated paralytic polio). We also offered a free text option for other unusual manifestations. There were 12 occurrences of vaccine-associated paralytic poliomyelitis with only one reported from Europe and none from North America (Table 4). There were 62 cases of arthritis and 10 of those were from Russia, a significant enrichment. Otherwise, there was no clear evidence of regional variation (Table 5).

Among the free text listings, none were listed more than once. Norovirus, campylobacter, and hepatitis C were each listed once as specific infections. Conjunctivitis, autoimmune enteropathy, cholangitis, autoimmune hemolytic anemia, and sarcoid were each listed once as inflammatory conditions.

Challenges reported by centers

We recognized that each center could have unique aspects related to patient care that were not predictable and we offered centers the opportunity to define their biggest challenges and unique patient features using a free text response (Table 6). Regionally unique aspects of care included mycobacterial infections in Argentina and India and vaccine-associated paralytic polio in countries that use the live polio vaccine (Table 4). The challenges were grouped according to the content of the free text. Centers were allowed to list up to three challenges. Immunoglobulin access, awareness of XLA/delay in diagnosis/diagnostic test access were the most common concerns listed at 16% of total responses each. Six centers listed cost to the patient as prohibitive or limiting. These centers were located in countries with incomplete government coverage and were located in North America, Asia, and Africa. Other common responses were compliance, quality of life issues and transition of care. Entero viral infections, inflammatory diseases, conjunctivitis and management of lung disease were listed by at least two centers. These concerns ranged from pragmatic aspects of patient care such as management of rare complications, to pleases for improved education regarding recognition of XLA, to government policy regarding immunoglobulin.

Discussion

To understand the current landscape of regional variation in XLA, we performed a survey to understand diagnostic approaches, available therapies and regional complications. This WAO survey achieved a remarkable reportage from 32 countries widely distributed around the world. This is the largest series of XLA patients reported to date. We compared our data to published series of patients with XLA (Table 7). Notable differences across reports were the frequency of neutropenia ranging from 1 to 22% among those who reported this feature. Meningoencephalitis was reported in 4–38% of patients at different centers although pathogens were rarely reported. Therefore, these could have represented entero viral disease, bacterial meningitis or autoimmune conditions. Our survey identified entero viral disease in 4.6% of patients consistent with that seen in other reports. Arthritis was reported in our survey in 7.9% while it was reported form other centers as 7–29%. Orchi tis, an unusual clinical feature in XLA, was reported in significant numbers from two centers and was not specifically queried in our survey. Thus, the data from this survey are consistent with previous

Table 4

Regional differences in XLA.

<table>
<thead>
<tr>
<th>Region</th>
<th>Survival &gt;20y of age</th>
<th>Entero viral meningoen cephalitis</th>
<th>Inflammatory bowel disease</th>
<th>Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa n = 229</td>
<td>22%</td>
<td>1.9%</td>
<td>1.3%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Asia n = 169</td>
<td>39%</td>
<td>0.59%</td>
<td>2.4%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Australia n = 7</td>
<td>&gt;75%</td>
<td>0</td>
<td>0</td>
<td>14.3%</td>
</tr>
<tr>
<td>Europe n = 186</td>
<td>&gt;75%</td>
<td>0.54%</td>
<td>5.9%</td>
<td>17.2%</td>
</tr>
<tr>
<td>North America n = 136</td>
<td>75%</td>
<td>0</td>
<td>2.2%</td>
<td>2.9%</td>
</tr>
<tr>
<td>South America n = 56</td>
<td>72%</td>
<td>10.7%</td>
<td>8.9%</td>
<td>7.1%</td>
</tr>
</tbody>
</table>

* Survival was based on a weighted average of reported categorical responses.

Table 5

Infrequent manifestations of XLA.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Cases reported</th>
<th>Percentage of reported cohort</th>
<th>Data from other publications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory bowel disease</td>
<td>27</td>
<td>3.4%</td>
<td>2.27%</td>
</tr>
<tr>
<td>Enteroviral meningoen cephalitis</td>
<td>36</td>
<td>4.6%</td>
<td>4.38%</td>
</tr>
<tr>
<td>Large granular lymphocyte disease</td>
<td>1</td>
<td>0.1%</td>
<td>–</td>
</tr>
<tr>
<td>Arthritis</td>
<td>62</td>
<td>7.9%</td>
<td>7–29%</td>
</tr>
<tr>
<td>Chronic cutaneous ulcers</td>
<td>6</td>
<td>0.8%</td>
<td>6–28%</td>
</tr>
<tr>
<td>Vaccine-associated paralytic polio</td>
<td>12</td>
<td>1.5%</td>
<td>1%</td>
</tr>
</tbody>
</table>

* Meningitis/encephalitis. Could be entero viral disease, bacterial meningitis or autoimmune conditions.

10 Reported as skin involvement.
<table>
<thead>
<tr>
<th>Country (Reference)</th>
<th>(N)</th>
<th>Age -presentation</th>
<th>Age at diagnosis</th>
<th>Presenting manifestation</th>
<th>FH</th>
<th>Pneumonia (%)</th>
<th>GI disease (%)</th>
<th>Meningitis/encephalitis</th>
<th>Otitis</th>
<th>Other</th>
<th>CLD (%)</th>
<th>Deaths (%)</th>
<th>BTK mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algeria¹⁴</td>
<td>9</td>
<td>15 m</td>
<td>6.7y</td>
<td>100% Respiratory infections</td>
<td>22%</td>
<td>100%</td>
<td>22%</td>
<td>22% Neutropenia</td>
<td>11% Arthritis</td>
<td>11% Skin infection</td>
<td>17%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iran¹⁵,¹⁶</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td>67%</td>
<td>27%</td>
<td>20%</td>
<td>20% Septic arthritis</td>
<td>13% JIA</td>
<td>10% Neutropenia</td>
<td>17%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morocco¹³</td>
<td>50</td>
<td>10 m</td>
<td>4y</td>
<td></td>
<td>32%</td>
<td>92%</td>
<td>42%</td>
<td>27%</td>
<td>47%</td>
<td>34%</td>
<td>15%</td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td>France¹⁷</td>
<td>31</td>
<td>7 m</td>
<td></td>
<td>84% Infections</td>
<td>16%</td>
<td>48%</td>
<td>10%</td>
<td>10% EnteroViral</td>
<td>13%</td>
<td>35%</td>
<td>15%</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>Italy¹⁸</td>
<td>73</td>
<td>3.5y</td>
<td></td>
<td>68% Respiratory infections</td>
<td>40%</td>
<td>53%</td>
<td>19%</td>
<td>4%</td>
<td>50%</td>
<td>48%</td>
<td>33%</td>
<td>1.4%</td>
<td>100%</td>
</tr>
<tr>
<td>Netherlands¹⁹</td>
<td>15</td>
<td>14 m</td>
<td>6.5y</td>
<td></td>
<td>100%</td>
<td>73% Gastroenteritis</td>
<td>27%</td>
<td>53%</td>
<td>67% Sinusitis</td>
<td>80%</td>
<td>33%</td>
<td>26.6%</td>
<td></td>
</tr>
<tr>
<td>Poland¹³</td>
<td>44</td>
<td>13 m</td>
<td>3.7y</td>
<td>73% Lower respiratory infections</td>
<td>59%</td>
<td>64%</td>
<td>14%</td>
<td>41%</td>
<td>27%</td>
<td>4.5%</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portugal¹⁵</td>
<td>9</td>
<td>13 m</td>
<td>3.4y</td>
<td>89% Infection</td>
<td>11%</td>
<td>56%</td>
<td>33%</td>
<td>Giardia</td>
<td>78%</td>
<td>33%</td>
<td>22%</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>Spain¹⁰, United Kingdom¹¹</td>
<td>30</td>
<td>23 m</td>
<td>6y</td>
<td></td>
<td>55%</td>
<td>62%</td>
<td>16%</td>
<td>17%</td>
<td>17%</td>
<td>6%</td>
<td>83%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>China¹⁵</td>
<td>62</td>
<td>24 m</td>
<td>7y</td>
<td></td>
<td>40%</td>
<td>73%</td>
<td>29%</td>
<td>13%</td>
<td>37%</td>
<td>29%</td>
<td>3%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Korea¹⁰</td>
<td>19</td>
<td>4.9y</td>
<td></td>
<td></td>
<td>31%</td>
<td>68%</td>
<td>16%</td>
<td>Gastroenteritis</td>
<td>32%</td>
<td>4%</td>
<td>5%</td>
<td>10.5%</td>
<td>42%</td>
</tr>
<tr>
<td>Mexico¹²</td>
<td>26</td>
<td></td>
<td></td>
<td></td>
<td>69%</td>
<td>19% Diarrhea</td>
<td>4% Colitis</td>
<td>38%</td>
<td>61%</td>
<td>57%</td>
<td>38%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>USA¹³</td>
<td>96</td>
<td>10 m</td>
<td>2.9y</td>
<td>65% Lower Respiratory 75% ENT</td>
<td>55%</td>
<td>65%</td>
<td>35%</td>
<td>16%</td>
<td>59%</td>
<td>28%</td>
<td>70%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>USA¹⁴</td>
<td>201</td>
<td>12 m</td>
<td>4y</td>
<td>86% Infection</td>
<td>58%</td>
<td>62%</td>
<td>23%</td>
<td>12%</td>
<td>70%</td>
<td>3%</td>
<td>9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FH: Family history; GI: gastrointestinal; CLD: chronic lung disease; JIA: juvenile idiopathic arthritis; VAPP: vaccine associated paralytic poliomyelitis.
patients but greatly expand the understanding of the overall landscape of patients with XLA.

Infections are a major clinical indicator of XLA. The original description by Colonel Ogden Bruton depicted a boy with recurrent sepsis, pneumonia and otitis media. Respiratory tract infections constitute a prominent and ongoing clinical problem despite immunoglobulin replacement therapy. In one study, the overall probability of developing chronic lung disease reached about 80% after 17 years of follow-up. Gastrointestinal disorders, mainly diarrhea were reported almost as often as lower respiratory tract infections in Poland whereas inflammatory bowel disease was diagnosed quite infrequently. In India, the most common infection noted was pneumonia. The summary of features from many countries in Table 7 highlights the continuing pattern of significant and life-altering infections. Chronic lung disease and sepsis were the two most common causes of death, in this survey, suggesting that management continues to fall short for some patients. Nevertheless, there is cause for cautious optimism as nearly all centers had access to immunoglobulin even if access was complicated and gaps occurred. Over half of the centers reported that the majority of their patients were reaching adulthood.

Patient survival was highly regional, reflecting healthcare challenges in countries with emerging economies. Several centers commented on the difficult logistics for patients with only a single center in some countries offering diagnosis and treatment. The Eurodis survey noted patients with rare diseases lack access to local care in many European countries. Improving education of the primary care physicians managing patients locally was a key need noted by several contributors. Efforts to provide printed materials in various languages could benefit many patients and increasing use of technology to support primary care physicians will be increasingly important. Lack of education is also related to delays in diagnosis. When primary care providers understand the clinical features they are more likely to refer for diagnostic testing. Although a number of efforts have been instituted to improve awareness and recognition of inborn errors of immunity, it appears that additional efforts could have a substantial benefit.

This study examined uncommon complications, leveraging the large sample size and the expertise of the contributors. In this regard, we were able to identify a higher than anticipated frequency of these complications collectively. Enteroviral disease, including vaccine-associated paralytic polio is still occurring (12 patients). This ruinous complication is likely related to delayed diagnosis. Whereas inflammatory bowel disease was diagnosed quite infrequently (1/44 (2.3%) in one center), this study showed a frequency of 3.4%. Complications such as cutaneous ulcers (often due to Flexispira or Campylobacter), inflammatory bowel disease, large granular lymphocyte disease and arthritis are not thought to be related to lack of treatment, although the specific risks for these infrequent complications are not known. Mycoplasma or Ureaplasma arthritis may occur more often in untreated or sub-optimally treated patients. The overwhelming sense from this survey is that these “infrequent” complications collectively affect a significant number of patients with XLA. Nearly 20% of patients had one of these “infrequent” complications. In the free text fields, centers noted struggles to treat unusual infections, unusual autoimmunity, and to coordinate multiple specialties for complex patients. These challenges are universal and not clearly related to geography, type of insurance, or size of the center. Our findings support development of a world-wide community of immunologists to share best practices for rare complications.

Our overall goal was to examine regional differences in diagnostic testing, therapies, and clinical manifestations. In fact, we uncovered relatively few regional differences with vaccine-associated paralytic polio being perhaps the only complication with a clear regional component, wholly related to exposure. Mycobacterial infections also seemed to have a regional effect.

We offered respondents the opportunity to describe their main challenges and many responses were not purely medical. Compliance with medications, transitioning of patients to adult providers and education of patients ranked very high among the cited challenges in our survey. As centers move from the original concern of keeping patients alive, now the focus has fittingly moved to optimization of health. These concerns were surprising because they require time and focus but little in the way of technology or other resources that are often limiting. There are few guidelines for the transitioning specifically for people living with inborn errors of immunity. Some progress has been made in developing guidelines for transitioning of children with chronic illness and these may be applied, although a destination adult-care clinic is still central to the process and often lacking. Limitations of this study are the use of a non-validated survey instrument that was focused on specific outcomes and questions. The aggregations of the free text responses may have imposed an interpretation not been intended by the responder. Additionally, this survey did not reach every country. There is likely additional heterogeneity in responses not captured in this survey. Representation from East Asia was relatively weak and Southern Africa was represented by a single center. Nevertheless, this study provides an important framework for strategically considering diagnostic testing and treatment approaches that could be mandated by the World Health Organization. The World Health Organization already includes immunoglobulin as an “Essential Medication.” This is the largest cohort of patients with XLA ever reported and provides critical information on medical concerns as well as challenges to meeting the next goal of a full and healthy life for all patients.

In summary, this survey conceptualized by the WAO in 2018, demonstrated key findings. Most patients are surviving to adulthood and infections continue to be the most frequent manifestation. Access to immunoglobulin replacement is fairly uniform but centers reported frustrations with lack of subcutaneous immunoglobulin, the high cost of immunoglobulin and the logistical aspects of obtaining and delivering immunoglobulin. This survey highlighted the less frequent complications and supports development of a multinational registry or communal blackboard to share treatment approaches and to study outcomes. Strategies to share practices on transitioning and education of primary care and other referral sources is a critical need and one in which resource sharing could be beneficial.

Conclusions

Survival of patients with XLA is good globally, however, this study revealed a surprising burden of morbidities with nearly 20% suffering from what have been considered unusual complications. Centers identified a number of challenges in providing care for patients including access to immunoglobulin in a manner that is financially achievable, logistically feasible, and respectful of patients’ time. Other challenges included education of patients and primary care physicians and the transitioning of patients to adult centers. Overall, this study supports better efforts to share best practices internationally, and suggests that there is much to be done to optimize patient care.

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Consent for publication

Not applicable.

Conflicts of interest

The authors declare that they have no competing interests.

Availability of data and materials

The dataset is available from Kathleen Sullivan.
Ethics

The Children’s Hospital of Philadelphia Institutional Review Board determined that data reported in aggregate did not require consent. I confirm that each author has contributed in a substantive and intellectual manner. This manuscript has not been submitted elsewhere. No commercial financial support was utilized. The authors declare that they have no competing interests.

ZAE-S, EH, and KES conceived and designed the study. ZAE-S and KES wrote the manuscript with assistance from all co-authors. JA, JCA, WA-H, LB, RB, AAB, CC, AC-N, GD, BD, JDME, BE, RHE-O, SEEP, NG, FH, RH-W, AI, EK, HK, NK, YLL, TM, VM, JFN, MO, RP, KP, CP, AP, FQN, SQ, NfN, NRe, NRo, JR, BS, AS, MRHS, EGS, AS, SSing, SSini, GS, MT, AMV, AV performed data analysis and review.

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