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Autoimmunity and Inflammation in X-linked Agammaglobulinemia

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Abstract

Purpose—In the past, XLA was described as associated with several inflammatory conditions, but with adequate immune globulin treatment, these are presumed to have diminished. The actual prevalence is not known.

Methods—A web-based patient survey was conducted December 2011- February 2012. Respondents were recruited from the Immune Deficiency Foundation (IDF) patient database,

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online patient discussion forums and physician recruitment of patients. The questionnaire was developed jointly by IDF and by members of the USIDNET-XLA Disease Specific Working Group. Information regarding inflammatory conditions in patients with XLA was also obtained from the United States Immune Deficiency Network (USIDNET) Registry.

Results—Based on 128 unique patient survey responses, the majority of respondents (69 %) reported having at least one inflammatory symptom, with 53 % reporting multiple symptoms. However, only 28 % had actually been formally diagnosed with an inflammatory condition. Although 20 % reported painful joints and 11 % reported swelling of the joints, only 7 % were given a diagnosis of arthritis. Similarly, 21 % reported symptoms of chronic diarrhea and 17 % reported abdominal pain, however only 4 % had been diagnosed with Crohn's disease. Data from the USIDNET Registry on 149 patients with XLA, revealed that 12 % had pain, swelling or arthralgias, while 18 % had been diagnosed with arthritis. Similarly, 7 % of these patients had abdominal pain and 9 % chronic diarrhea.

Conclusions—Although patients with XLA are generally considered to have a low risk of autoimmune or inflammatory disease compared to other PIDD cohorts, data from this patient survey and a national registry indicate that a significant proportion of patients with XLA have symptoms that are consistent with a diagnosis of arthritis, inflammatory bowel disease or other inflammatory condition. Documented diagnoses of inflammatory diseases were less common but still increased over the general population. Additional data is required to begin implementation of careful monitoring of patients with XLA for these conditions. Early diagnosis and proper treatment may optimize clinical outcomes for these patients.

Keywords

X-linked agammaglobulinemia; primary immunodeficiency; antibody deficiency; autoimmune; inflammation

Introduction

X-linked agammaglobulinemia (XLA) is caused by a B lymphocyte differentiation arrest associated with mutations in the *BTK* gene located on the long arm of the X chromosome [1, 2]. Primary Immune Deficiency Diseases (PIDDs), including XLA, usually manifest with frequent, recurrent or persistent infections. Patients with XLA are highly susceptible to infections with encapsulated organisms such as *S. pneumoniae*, *Pseudomonas spp*. and *H influenzae*, but also giardia, mycoplasma and enteroviruses [3, 4]. While many PIDDs, in particular common variable immune deficiency (CVID), chronic granulomatous disease (CGD), Wiskott Aldrich Syndrome (WAS), Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked syndrome (IPEX), and the Hyper IgM Syndromes, are often associated with a variety of autoimmune conditions and/or formation of autoantibodies [5, 6], subjects with XLA, on adequate immunoglobulin replacement, are generally considered to be spared these inflammatory conditions and have a good quality of life [7]. Patients with XLA, especially at the time of diagnosis and in association with acute infections, may have neutropenia; however, overall, other cytopenias have not been reported and the neutropenia is not thought to be autoimmune in nature [8]. Early reports of arthritis in XLA patients are now often ascribed to mycoplasma or other infections, likely due to insufficient immune

globulin treatment [3, 9, 10]. Intermittent reports of other autoimmune/inflammatory conditions have appeared in the literature, suggesting that inflammatory conditions may occur at a low frequency. The purpose of this study was to define the prevalence and type of inflammatory symptoms and diagnoses in XLA patients now that immunoglobulin replacement is more standardized and effective.

Methods

The patient survey instrument and the USIDNET query were structured to collect symptoms that could be ascribed to common autoimmune and inflammatory conditions such as arthritis, colitis/enteritis, and cytopenias. Because the etiology could never be verified in a survey methodology, we will refer to the conditions collectively as inflammatory conditions. Respondents to the patient survey were self-described as having XLA, while the USIDNET cases were physician-verified cases. Among the USIDNET cases, 100 % had CD19 B cells <2 % and 67 % were described as “definitive” XLA cases.

The Patient Survey

A non-incentivized Web-based survey of patients with XLA was conducted from December 2011 through February 2012. The questionnaire was developed jointly by Immune Deficiency Foundation (IDF) and by members of the United States Immune Deficiency Network (USIDNET)-XLA Disease Specific Working Group to investigate the frequency of symptoms related to potential inflammatory conditions. It was distributed by the IDF and by physician outreach. It was promoted on IDF Friends, Facebook XLA Group, and a Yahoo XLA Group as well as a direct email from the IDF. The 27-question survey included questions about symptoms, conditions, concurrent diagnoses, medications (including antibiotics and immunoglobulin replacement therapy). The survey included yes or no questions, multiple choice questions, fill in the blanks and open text fields. This resulted in 128 unduplicated completions from both adult and pediatric XLA patients.

Data from the USIDNET Registry

To provide validation and comparison with the patient survey, we also compiled comparable data from the records entered into the USIDNET Registry. The USIDNET Registry is an online system accessed through an internet link: http://www.usidnet.org. It contains a core Registry form for all PIDDs, and disease-specific forms for CVID, hyper-IgM syndromes, CGD, combined and severe immune deficiency (CID and SCID), complement disorders, WAS, NFκB essential modulator (NEMO) deficiency, DiGeorge syndrome and XLA. Entry of patient data requires approval of an IRB at the institution where the patient receives care, or the IRB with which USIDNET has established an affiliation. Data is entered by physicians or their designees, or the staff of USIDNET may abstract such data from physician records. The Registry is comprised of 850–1,000 fields containing both clinical and laboratory data. Records of the entered XLA patients were extracted, selecting for fields related to inflammatory conditions. USIDNET data is audited regularly and discrepant fields are corrected after querying the entering physician or redacted if correction is not possible. The error rate at the last audit was 0.6 %.

Statistics

To examine the data from these sources, descriptive statistics and the Fisher's Exact test were used where appropriate.

Results

Patient-Reported Survey

The patient survey was returned by 44 adults with XLA and by 84 parents on behalf of their children. Thus, surveys for 128 subjects were available. Of 45 patients who answered this question, the average age of these patients was 17.6 years, with a range of 1 to 50 years. Based on 128 unique responses, 69% of the cases had one or more symptoms suggestive of an inflammatory condition; 53 % of these reported multiple symptoms, with a mean of 3.6 symptoms. Individual conditions were found between 2–27 % of subjects (Table I). For example, 21 % reported chronic diarrhea or skin rashes, 20 % had joint pain and 11 % noted joint swelling.

Although a number of subjects reported symptoms compatible with joint disease, only 7 % had been formally diagnosed with arthritis (Table II). Specifically, 2%reported being diagnosed with rheumatoid arthritis with 5 % having "other" arthritis. While a number of subjects had gastrointestinal complaints, the cause of this appeared to be unknown, with only 4 % diagnosed with Crohn's disease. Patients also reported being diagnosed with hematologic diseases such as thrombocytopenia (3 %), leukopenia (6 %) and anemia (10 %), more often autoantibody-mediated but possibly due to infection in this population.

Infections have been associated with inflammatory changes in normal hosts and are thought to contribute to a breach in tolerance, therefore, we investigated the frequency of infections. Although all of the patients were on replacement immunoglobulin therapy, and 70 % believed that this therapy controlled infections, a significant proportion of the survey respondents reported one or more infections in the past 12 months. Almost 40 % of the patients reported the use of prophylactic antibiotics to prevent infections. Most commonly, patients reported using co-trimoxazole, amoxicillin or amoxicillin-clavulanic acid.

USIDNET Registry Data

We queried the USIDNET Registry to provide a set of alternative data for comparison. The data in the registry represent physician-verified diagnoses as well as patient-reported symptoms. The average age of these patients was 31.4 years, with a range of 1 to 66 years. The majority of patients were white/ Caucasian (76 %) with fewer patients of African-American (12 %), Hispanic (10 %), Asian (2 %) and Native American (1 %). As was true in the patient survey, a variety of inflammatory symptoms were recorded. Joint complaints were common with 12 % having joint pain, swelling or arthralgias, and 16 % diagnosed with arthritis. Gastrointestinal complaints were also common with 7 % having abdominal pain and 9 % having chronic diarrhea. Only 3 % were diagnosed with enteritis or colitis. XLA patients in the USIDNET Registry also were reported to have hypothyroidism/goiter (5 %) and vasculitis (1 %).

Comparison of Patient-Reported Symptoms and USIDNET Registry Data

There was an overlap between the surveyed patients, and the USIDNET Registry; 15 % of those in the XLA survey also reported being part of the USIDNET Registry. Significantly more patients in the patient survey reported aches, malaise or fatigue, chills or shortness of breath, as compared to those reported in the USIDNET Registry (Table III, $p < 0.001$). While similar numbers of patients in both the patient survey and the USIDNET Registry were reported to have had thrombocytopenia or neutropenia, 10 % reported anemia in the patient survey, as compared to 4 % in the USIDNET Registry. On the other hand, one patient in the USIDNET Registry had been diagnosed with vasculitis, while no surveyed patient reported this diagnosis.

Discussion

Autoimmune and/or inflammatory diseases are characteristic of many primary immune deficiencies affecting different parts of the immune system. The postulated mechanisms range from impaired clearance of apoptotic cells to diminished tolerance and compromised regulatory T cell function. Patients with XLA would not be expected to produce autoantibodies, although defective B cell tolerance has been described and “leaky” production of autoantibodies could theoretically occur [11]. T cells are felt to be functionally normal in XLA. Myeloid cells on the other hand, have had demonstrable functional deficits reported due to the role of BTK in the transduction of TLR signals [12, 13]. This has been postulated to contribute both to infection susceptibility and to a predisposition to inflammatory conditions.

In patients with CVID, the most common of the antibody defects, autoimmune cytopenias, granulomatous lung disease, inflammatory bowel disease, and rheumatoid arthritis are common; and autoimmunity confers a worse prognosis in patients with CVID [14–16];[13]. CVID patients have a more globally dysregulated immune system and while autoimmunity and inflammation have received attention, it has been felt that these were uniquely associated with CVID [17–20].

To better understand the frequency of inflammatory diseases in XLA, this study took a two-pronged approach. We reasoned that patients would have a more comprehensive perspective on symptoms while physicians might be able to provide insights into classically diagnosed inflammatory conditions. Patients had a surprisingly high rate of symptoms, with fatigue occurring in 34 %, comparable to that seen in rheumatoid arthritis [21]. Diarrhea and musculoskeletal pain comprised the other high frequency symptoms. Not surprisingly, patient-reported symptoms generally exceeded those reported by physicians. Aches, chills, shortness of breath, constipation, diarrhea, abdominal pain, and joint pains were all reported significantly more commonly by patients than in the registry. This disconnect has been seen in other clinical settings [22]. The shortness of breath is worrisome, however, as progressive lung disease has been observed in XLA [7, 23, 24]. In terms of physician diagnoses, there was good concordance for intestinal inflammation. Crohn’s disease was diagnosed in 3.4 % of patients in the survey. This was comparable to the IBD/enteritis frequency in the USIDNET registry of 3.4 %, and significantly above the population prevalence of 0.4 % [25]. In terms of joint inflammation, 2 % of patients reported a diagnosis of rheumatoid

arthritis with 5 % having “other” arthritis. This was lower than the frequency of arthritis at 16 % in the USIDNET Registry, which excluded septic arthritis. A potential explanation is the higher age of the Registry patients and the inclusion of patients who were initially treated with intramuscular immunoglobulin. Collectively, these data support a moderately high frequency of symptoms that could reflect an underlying inflammatory condition. A low but significant frequency of diagnosed inflammatory conditions was seen as well.

Limitations to this study include the use of a patient survey, with possible recall bias or overestimation of self-reported symptoms by patients. Imprecision inherent in the nomenclature can be problematic in surveys. For example “fatigue” is highly subjective to patients, and to physicians may refer to muscle fatigue. Although surveys present unique limitations, they are also a powerful tool in obtaining invaluable information. The Registry data was also limited as it may underestimate the presence of intermittent symptoms or diagnoses, that the patient is aware of but not reported in the clinical record. The electronic Registry, which went “live” in 2008, is still being populated with longitudinal data, thus the Registry data may lack serial time points needed to follow the patients over time. It was not possible to determine which of the patients participating in the survey were also part of the USIDNET Registry. Since the Registry reported the presence of some forms of inflammatory disease in XLA, that were not reported by the patients themselves, such as vasculitis, the strategy of obtaining information from both the patient survey and the Registry was advantageous. The fact that many patients had symptoms present without carrying a diagnosis highlights the importance for clinicians who care for these patients to be aware that inflammatory disease may be present in these patients. Additional controlled studies of a larger sample size may be required to define the precise frequencies of inflammatory co-morbidities in XLA, but this study represents an important window into this neglected set of conditions.

In this sample of patients with XLA, cases of Crohn’s colitis, anemia, thrombocytopenia and neutropenia exceed the expected prevalence of these disorders in the general population. This study highlights the importance of considering the presence of inflammatory disorders in patients with XLA, treatment of which would be expected to decrease morbidity and optimize patient outcomes.

Conclusions

Use of both a patient survey and USIDNET Registry data was important in gaining a better understanding of the association of inflammatory disease in XLA. A low but significant signal for inflammatory diseases was seen.

Abbreviations

USIDNET	United states immune deficiency network
XLA	X-linked agammaglobulinemia

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Table I

Patient self-reported symptoms[1]

Symptom	N (%)
Fatigue	44 (34.4)
Chronic diarrhea	27 (21.1)
Rash/skin problems	27 (21.1)
Painful joints	25 (19.5)
Fevers	23 (18.0)
Abdominal pain	22 (17.2)
Weakness	22 (17.2)
Shortness of breath	21 (16.4)
Sweats	20 (15.6)
Muscle Pain	18 (14.1)
Back pain/stiffness	18 (14.1)
Chronic headaches	18 (14.1)
Chills	17 (13.3)
Weight loss	16 (12.5)
Constipation	14 (10.9)
Swelling of joints	14 (10.9)
Weight gain	11 (8.6)
Nausea/vomiting	10 (7.8)
Frequent urination	9 (7.0)
Tremors/shaking	9 (7.0)
Numbness	9 (7.0)
Blood in urine	7 (5.5)
Swelling (feet)	7 (5.5)
Swelling (hands)	6 (4.7)
Bloating	6 (4.7)
Racing heart beat	5 (3.9)
Warm joints	4 (3.51)
Bloody stools	3 (2.3)
Rectal bleeding	2 (1.6)
Other symptoms	29 (22.7)

[1] 128 respondents. 31 % reported no symptoms with a mean of 3.6 and a median of 2 symptoms

Table 2

Patient self-reported diagnoses[1]

Diagnosis	N (%)
Rash/skin problems	13 (11.6)
Low red blood cell count	11 (9.8)
Chronic diarrhea	9 (8.0)
Low white blood cell count	7 (6.3)
Other arthritis	6 (5.4)
Crohn's Disease	4 (3.6)
Low platelets	3 (2.7)
Rheumatoid arthritis	2 (1.8)
High blood sugar	1 (.8)
Insulin dependent diabetes	1 (.8)
Kidney disease	1 (.8)

[1] N=112 respondents

Table III

Comparison of USIDNET and patient-reported data

Reported Condition	USIDNET N=149	Survey N=128	p Value
Aches, malaise or Fatigue	22 (14.8)	44 (34.4)	0.001
Chills	1 (.7)	17 (13.3)	0.001
Shortness of breath	1 (.7)	21 (16.4)	0.001
Constipation	3 (2.0)	14 (10.9)	0.002
Diarrhea (chronic)	13 (8.7)	27 (21.1)	0.005
Abdominal pain	10 (6.7)	22 (17.2)	0.008
Pain, swelling arthralgia	18 (12.1)	28 (25.0)	0.035
Abdominal bloating	1 (.7)	6 (4.7)	0.051
Hyporthyroidism/Goiter	5 (3.4)	0 (0)	0.064
Colitis/enteritis	4 (2.7)	0 (0)	0.126
Anemia/hemo-anemia	6 (4.0)	11 (9.8)	0.135
Renal Issues	5 (3.4)	1 (.9)	0.221
Neutropenia	7 (4.7)	7 (6.3)	0.790
Diabetes	2 (1.3)	1 (.8)	0.999
ITP/Thrombocytopenia	3 (2.0)	3 (2.7)	0.999
Vasculitis	1 (.7)	0 (0)	0.999
Diarrhea (intermittent)	15 (10.1)	NA	NA
Gastroenteritis	11 (7.4)	NA	NA
IBD	1 (.7)	NA	NA
Arthritis	24 (16.1)	NA	NA
Infectious arthritis	3 (2.0)	NA	NA