X-linked agammaglobulinemia (XLA) is a primary humoral immunodeficiency caused by pathogenic variants of the gene that leads to defective or absent expression of Bruton Tyrosine Kinase (BTK), which is a signal transduction molecule involved in B-cell maturation. This results in low to absent mature B-lymphocytes and, consequently, significantly decreased immunoglobulins of all classes. Without the ability to properly opsonize and neutralize pathogens, patients with XLA experience serious illnesses caused by encapsulated organisms, most commonly upper respiratory tract infections. Diagnosis of XLA is based on clinical history, family history, and laboratory tests: recurrent infection with low immunoglobulin level, family history of XLA in maternal male relatives, and confirmed BTK gene mutation.

Case Description

History

In this report, we present a 3-year-old male, who presented with a 2-day history of fever, recurrent non-bilious, non-bloody emesis, diarrhea, altered mental status, and inability to sit or stand. The patient was found to have Hemophilus influenzae meningitis and bacteremia, complicated by septic arthritis of the left hip joint and Bocavirus infection.

Past Medical History: The patient was born full-term and had a normal newborn screen. Other than pulmonary valve stenosis diagnosed at two months of age, he was overall healthy until he turned three years old. The patient had three episodes of ear infections and community-acquired pneumonia that were treated with oral antibiotics. In addition to pre-septal and orbital cellulitis, this is the first serious bacterial infection that required hospitalization.

Further history revealed a male sibling who died in childhood from intra-abdominal infection, possibly from a ruptured appendix. He has two other healthy male siblings. Mom also reported her two male siblings passed away of unknown etiology at three and eight years of age.

Methods

Review of Literature

• More than 600 BTK mutations have been reported on BTKbase published in 2006. Additional novel mutations of the gene continue to be identified. In our study, we searched PubMed for case reports published in the past 10 years using keyword “BTK mutation XLA.” We found 97 articles on PubMed pertaining to BTK mutation and XLA, of which 23 noted novel mutations. To our best knowledge, nonsense mutation c.1361A>C (p.His454Pro) has not yet been reported.

• According to the international survey done by World Allergy Organization, delay of diagnosis greater than 24 months was reported by 34% of the centers that participated in the survey1. Another multicenter study done by Plebani et al. shows increased age at diagnosis is associated with higher risk of developing complications of XLA, such as chronic lung disease2. Diagnostic delay is thought to be due to atypical presentation or nearly normal levels of serum immunoglobulins.

Case Description

• Variation in disease severity is a well-known phenomenon among XLA patients. Lopez-Granado et al. demonstrated the association between the type of mutation and disease severity using flow cytometry and Western blot3. Lopez-Granado’s group classified the mutation in terms of immunoglobulin level. However, they also identified phenotype variability even with identical genotypes. Both Lopez-Granado’s and Plebani’s groups showed multiple patients with identical mutations had different levels of immunoglobulin levels, indicating a possible involvement of other genetic or epigenetic factors that determine phenotype4,5. Plebani et al., therefore, suggests percentage of circulating B cell might be a better indicator of XLA than immunoglobulin level.

Work-up

• Immune workup showed severely low IgG, IgA, and IgE levels. Unexpectedly, patient was making IgM (table 2).
• The lymphocyte subset panel showed a high level of CD3, nearly absent natural killer cells (1%), and absent CD19+ B lymphocytes (0%).
• Additional immunological workup:
  - Normal neutrophil oxidative burst: NOI of 224
  - Additional bloodwork:
    - Low normal complement C3 (72 mg/dL) and C4 (14.5 mg/dL)
    - Imaging studies:
      - MRI of the Brain showed FLAIR hyperintensity diffusely throughout the subarachnoid spaces and subtle diffuse leptomeningeal contrast enhancement. There is diffuse paranasal sinus and mastoid opacification. Findings are consistent with acute meningitis, paranasal sinustis, and mastoiditis.
      - Ultrasound of the joint showed left hip joint effusion.
• The patient was diagnosed with XLA and responded well to IVIG therapy. IgG levels improved from less than 34 mg/dL to 949 mg/dL after multiple IVIG infusions.
• During outpatient follow-up, the Patient’s five-year-old sibling underwent a genetic work-up and was found to have the identical mutation as the patient, yet he had nearly normal IgG (425 mg/dL) and low levels of IgA (25 mg/dL) and IgM (10 mg/dL).

Results

Table 1. Initial lab studies: CBC and inflammatory markers

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<thead>
<tr>
<th>Cell Type</th>
<th>Reference Range</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>25-75%</td>
<td>79%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>20-40%</td>
<td>31.3%</td>
</tr>
<tr>
<td>Reactive Protein</td>
<td>40-180 mg/dL</td>
<td>1217</td>
</tr>
<tr>
<td>C-Reactive Protein</td>
<td>0-5 mg/dL</td>
<td>341</td>
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</tbody>
</table>

Table 2. Quantitative Immunoglobulin analysis

<table>
<thead>
<tr>
<th>Immunoglobulin</th>
<th>Reference Range</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>&lt; 34 mg/dL</td>
<td>341</td>
</tr>
<tr>
<td>IgA</td>
<td>&lt; 7 mg/dL</td>
<td>48</td>
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<tr>
<td>IgM</td>
<td>44 mg/dL</td>
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</tr>
<tr>
<td>IgE</td>
<td>19.9 mg/dL</td>
<td>&lt; 59 IU/ml</td>
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</tbody>
</table>

Discussion

This case highlights the importance of recognizing XLA as a diagnosis in children with recurrent infections. The patient’s older sibling with the same mutation but a milder phenotype speaks to the heterogeneity of this mutation. The question regarding the need for the proband’s sibling for surveillance lab testing remains unanswered without a clear protocol.

In conclusion, it is essential to maintain a high index of suspicion for XLA in children with recurrent infections, especially in the setting of unusual presentations. Early diagnosis and timely initiation of IVIG therapy can prevent such adverse events and their sequelae. Therefore, one should suspect XLA even if the disease manifestation deviates from well-established findings.

Conclusions

Our proband and his brother demonstrate phenotypic variations of a novel mutation and delay of XLA diagnosis due to unusual history. Aside from acute otitis media and community-acquired pneumonia treated in an outpatient setting, the patient had normal growth without neutropenia until three years of age. It is also worth noting his normal IgM level, albeit a bit low. Such a leaky phenotype might have contributed to the diagnostic delay. Our patient’s deceased brother and uncles may have had XLA. His older sibling has the same mutation but a milder phenotype, which speaks to the heterogeneity of this mutation. The question regarding the need for the proband’s sibling for surveillance lab testing remains unanswered without a clear protocol.

Diagnostic delay can lead to life-threatening infections, as seen in our patient, as well as long-term complications. Timely diagnosis, initiation of IVIG therapy, and antibiotic prophylaxis can prevent such adverse events and their sequelae. Therefore, one should suspect XLA even if the disease manifestation deviates from well-established findings.

Lastly, the data on BTK mutation in XLA patients with LatinX ethnicity is limited. A worldwide, multicentric study on XLA’s association with race and ethnicity is needed.

References