B Cells and COVID-19: Lessons From Patients With Agammaglobulinemia and the Study of Functional B-Cell Polymorphisms

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The SARS-CoV-2 pandemic (corona virus disease 2019, COVID-19) is one of the greatest challenges in modern medicine. It is noteworthy that not all individuals affected by SARS-CoV-2 display a specific pattern of infection; approximately 40% of infected individuals are completely asymptomatic, 40% display mild flu-like disease, and the remaining 20% present a more severe clinical phenotype, with one quarter of these individuals developing severe respiratory disease, characterized by pneumonia and/or severe acute respiratory distress syndrome [1]. Older age (over 65 years), obesity, hypertension, and chronic inflammatory diseases constitute the most important risk factors and are related to the development of serious sequelae and poor outcome [1]. Studies trying to explain the unfavorable prognosis of COVID-19 focus mainly on the role of immunosenescence or chronic inflammatory status [2] and address the respective therapeutic approaches [3]. However, the specific mechanisms implicated in prognosis remain unclear.

B cells represent a significant arm of immunity against pathogens and are particularly relevant in COVID-19, where the production of neutralizing antibodies acts as a major defense mechanism by eradicating the virions and providing immunity to the host [4]. However, Quinti et al [5] recently described 2 patients with agammaglobulinemia who displayed remarkably mild disease of short duration and with no requirement for treatment, suggesting that the inflammatory functions of B cells may contribute to the deterioration of COVID-19 disease and that their control could block cytokine production, thus improving disease outcome [5].

In this context, we further describe the clinical presentation of 3 Greek patients with X-linked agammaglobulinemia (XLA) infected by COVID-19. Furthermore, we used molecular assays described elsewhere [6] to describe the potential contribution of the most common functional polymorphisms of B cells, namely, BAFFR-P21R (rs77874543) and BAFFR-H159Y (rs61756766), to the clinical phenotype of 240 COVID-19 patients (male/female, 165/75; mean [SD] age, 40.6 [2.2] years). Patients were divided into 5 groups according to the severity of their disease, as follows: (a) asymptomatic, (b) mild without requiring hospitalization, (c) moderate requiring hospitalization, (d) severe with pneumonia, and (e) severe with SARS (requiring admission to the intensive care unit) (Supplementary Table 1). Written informed consent was obtained from all participants. The study was approved by the Ethics Committee of the School of Medicine, University of Thessaly (No. 2115) and was carried out in accordance with the principles of the Declaration of Helsinki.

The XLA patients presented at our outpatient clinics after molecular confirmation of the presence of viral SARS-CoV-2 RNA based on nasopharyngeal swab tests. Remarkably, their condition ranged from absence of disease to mild clinical disease without hospitalization, they did not receive any treatment (except for a patient receiving paracetamol once for fever), and they recovered quickly following SARS-CoV-2

Table. Demographic, Genetic, and Clinical Data of XLA Patients

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Genetic defect</th>
<th>XLA treatment and comorbidities</th>
<th>Clinical symptoms of COVID-19</th>
<th>Duration of COVID-19 symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>Male</td>
<td>c.1174_insA</td>
<td>fSCIG 30 g/4 wk, tension</td>
<td>Fatigue, no fever</td>
<td>1 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(frameshift defect)</td>
<td>headache for the last 2 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>Male</td>
<td>c.1700C&gt;T, p.A567V</td>
<td>fSCIG 25 g/3 wk, no</td>
<td>Headache,</td>
<td>1 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(missense mutation)</td>
<td>comorbidities</td>
<td>fever (over 37.6°C)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>Male</td>
<td>c.519_insC&gt;TGCATTGAGA</td>
<td>fSCIG 30 g/3 wk, no</td>
<td>Headache, runny nose,</td>
<td>2 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(frameshift defect)</td>
<td>comorbidities</td>
<td>fever (over 37.8°C)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: XLA, X-linked agammaglobulinemia.
infection (Table). Interestingly, their relatives exhibited a more severe COVID-19 course, although none needed hospitalization. Finally, the 3 XLA patients were negative for SARS-CoV-2 on the 12th, the 15th, and the 15th day, respectively, after their initial diagnosis.

As for functional polymorphisms in BAFFR, P21R affects BAFFR-dependent survival and activation of B cells, also predisposing P21R carriers to primary antibody deficiencies [7], whereas H159Y counteracts the function of P21R, resulting in sustained overactivated BAFF signaling [8,9]. In our cohort of 240 COVID-19 patients, 27 (11.7%) were heterozygous for the P21R polymorphism, and 3 of the P21R-carrying patients (1.2% out of the total) were also heterozygous for the H159Y polymorphism. We did not observe any significant differences in genotype or allele frequency between the subgroups of patients according to their clinical phenotype (Supplementary Table 1).

Therefore, we demonstrated the absence of a severe clinical phenotype in XLA patients with COVID-19, as well as the absence of an association between BAFFR polymorphisms and prognosis. XLA is caused by mutations in the BTK gene, and patients present with low to absent B cells in the periphery and agammaglobulinemia, experiencing severe and recurrent infections from infancy [5,10]. As previously mentioned, Quinti et al [5] also described 2 agammaglobulinemia patients with extremely mild COVID-19 disease [5]. However, Ho et al [10] reported 3 XLA patients with more severe disease who required hospitalization and supportive treatment, although even these patients exhibited reduced inflammatory responses and better outcomes than patients with other types of primary immunodeficiencies. Finally, Soresina et al [11] reported 2 adult XLA patients with COVID-19 who developed interstitial pneumonia but did not require oxygen ventilation or admission to the intensive care unit [11].

While we do not currently have a clear explanation for our findings, we can exclude the possibility that replacement immunoglobulin treatment had an impact on the prognosis of COVID-19, since patients with other antibody deficiencies under replacement treatment displayed a more severe clinical phenotype [5,10]. Therefore, we suggest that BTK signaling may primarily contribute to the prognosis of COVID-19, since BTK is also expressed by monocytes and dendritic cells and the impairment of BTK signaling also results in severe consequences for the innate immune response [12,13]. Thus, BTK-dependent activation of NF-κB and NLRP3 results in the production of proinflammatory cytokines such as IL-1β and IL-6 (which also contribute to the pathogenesis of COVID-19 [14,15]), while inhibition of BTK dampened the inflammatory response [12,13]. This notion is also supported by recent studies reporting favorable outcomes in patients with B-cell malignancies and COVID-19 who were receiving BTK-inhibitors (BTKi) (reviewed by Stack et al [13]). As a result, ongoing clinical trials are investigating BTKi in COVID-19 patients (ClinicalTrials.gov Identifier: NCT04528667, NCT04440007, NCT04439006) and should further elucidate their possible therapeutic effects. However, considering that other studies reported that BTK deficiency and inhibition enhance inflammation [13], it is obvious that the exact role of BTK signaling in the innate immune response needs to be further explored.

Therefore, we could speculate that the “inability” of B cells, monocytes, and dendritic cells to produce proinflammatory cytokines in both XLA patients and patients receiving BTKi may cause the mild COVID-19 phenotype. Our data support the notion that BTK signaling contributes to the inflammatory process of COVID-19, suggesting that dampening this process could be a therapeutic target, thus improving disease outcome.

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**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**References**


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