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Letter to the Editor

Most Important Factors in Diagnosing Cryopyrin-Associated Periodic Syndrome

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▸ See the article "The First Case Series of Cryopyrin-Associated Periodic Syndrome in Korea" in volume 11 on page 583.

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To the Editor,

Han *et al.*[1] recently reported a case series of patients with cryopyrin-associated periodic syndrome (CAPS). In their study, the authors stated that this was the first case series in Korea. Furthermore, genetic tests were carried out in patients with arthralgia, fever, and urticaria. We would like to voice concerns about this case series.

First, we are unsure as to whether this study is truly the first reported case series in Korea because Kim *et al.*[2] published an article that analyzed clinical manifestations and genotypes of 9 Korean children with CAPS in November 2018.

Secondly, we are concerned about the correct diagnosis because the patients in this study did not show any CAPS-typical symptoms. Han *et al.*[1] made a diagnosis according to the CAPS diagnostic criteria proposed by Kuemmerle-Deschner *et al.*,[3] which does not include *NLRP3* variants, and they stated that an urticaria-like rash was histologically characterized by neutrophilic dermatitis because the urticaria criterion has low specificity. We could not find any evidence of typical CAPS urticaria-like rash, which can be easily differentiated from cold urticaria by a simple ice cube test and non-responsiveness to an antihistamine agent.

Thirdly, genotype data were not corroborative for the confirmative diagnosis of CAPS. Instead, the authors cited a previous study by Houx *et al.*[4] to support the pathogenic potential of the p.Gly303Asp variant detected in patient 1. However, Houx *et al.*[4] reported a different variant, p.Asp303Asn, but not p.Gly303Asp, leaving the pathogenic potential of p.Gly303Asp unproven. This discrepancy could have been attributed to the use of different reference sequences of *NLRP3* between the 2 studies. Furthermore, the *NLRP3* variant in patient 3 is known as a variant of uncertain significance, and the possibility of a benign variant cannot be excluded.

Finally, Han *et al.*[1] reported that the anti-interleukin (IL)-6 receptor antibody (tocilizumab) therapy was effective in patient 3. Most patients treated with tocilizumab have normal serum levels of C-reactive protein (CRP) because IL-6 is an essential cytokine that induces CRP production in hepatocytes. It is thought that the normal serum levels of CRP are markers not for disease activity but for a sufficient concentration of tocilizumab which inhibits

IL-6 function.[5] Tocilizumab therapy has been reported in a patient with chronic infantile neurologic cutaneous articular syndrome/neonatal-onset multisystem inflammatory disorder. However, Snegireva *et al.*[6] reported that tocilizumab was not effective in such patients because CAPS is an IL-1mediated disease with a marginal increase in the levels of circulating IL-6.[7] Therefore, we request the authors further data to carefully demonstrate the effect of tocilizumab in CAPS.

We agree that we should consider CAPS as a probable diagnosis when we encounter patients with periodic fever, urticaria-like rash, arthritis/arthralgia, hearing problems, and bone destruction, which do not respond to conventional treatment as Han *et al.*[1] suggested in their paper. However, in our opinion, typical CAPS symptoms are the most important piece of evidence when diagnosing CAPS, and genetic studies are supportive methods, since not all CAPS subjects carry detectable *NLRP3* variants probably due to mosaicism.

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