Letters to the Editors

Comment on: Unexpectedly high prevalence of primary immune deficiency in fibromyalgia: serologic features and clinical correlates

Sirs,

In an issue of the 40th volume of *Clinical and Experimental Rheumatology*, we read the article of Caro and Winter (1). We thank the authors for their valuable research in which they analysed the levels of serum IgA, IgG, IgM, IgE, mannose-binding lectin levels and subclass concentrations for IgA, IgG in fibromyalgia (FM) patients. In conclusion they found 3 or more immunoreactants below the lower limits of normal (LLN) or within the lowermost quartile of historical normal values in most of the patients and they defined this result as a high prevalence of primary immune deficiency (PID) in FM patients. Although this is a straightforward and well-designed study, we wish to mention some points.

Primary immunodeficiency diseases are a growing group of diseases which were classified under 10 main groups. 485 diseases were defined within this disease group with the last update made by the International Union of Immunology Societies Expert Committee in 2022 (2). After IgA deficiency CVID is the most common PID in adults (3). The newest ESID criteria for CVID diagnosis include; a marked decrease of IgG (at least 2 SD below the mean for age) and a marked decrease in at least one of the isotypes IgM or IgA, and fulfils all of the following criteria:

1. Onset of immunodeficiency at greater than 2 years of age;
2. Absent isohaemagglutinins and/or poor response to vaccines;
3. Defined causes of hypogammaglobulinaemia have been excluded (4).

The authors declared that they used the adult LLN and range standards suggested by Schroeder *et al*. to define PID but they did not mention about the accurate diagnosis, clinical features, clinical course and treatment or immunoglobulin replacement therapy indications of the patients (5). But as we explained above, low immunoglobulin levels alone are not sufficient to diagnose a patient with PID. In addition, in the international nomenclature there is not a definition of PID as IgA subclass deficiency or IgE deficiency. On the contrary, there is a definition of PID as hyper IgE syndrome (2).

Secondly, for the final diagnosis of PID, the secondary causes of immunodeficiency must be excluded. Secondary immunosuppression causes such as HIV infection, lymphatic malignancies, malnutrition, renal failure, hepatic disease or hypogammaglobulinemia secondary to loss like in protein-losing enteropathy, nephrotic syndrome, severe burns, hyper catabolism are the remarkable causes of secondary immunodeficiency which the authors did not note in the article (3, 6). Also, certain drugs such as rituximab, glucocorticoids, carbamazepine, phenytoin, captopril, fenclofenac, sulfasalazine, penicillamine, gold salts or antimalarial agents may cause secondary hypogammaglobulinemia (7). As stated in the article, 41 of 72 patients have the diagnoses of rheumatoid arthritis. But the authors did not mention about the therapy history of these patients or whether the decreased Ig levels were checked before or after treatment. Therefore, although they refer to it as primary in the title of the article, the deficiencies detected can also be secondary.

Lastly, the researchers only examined the alternative pathway of the complement. Mannose-binding lectin (MBL) measurement is usually not helpful because MBL deficiency is commonly seen in general population (up to 5%) and only MBL deficiency is not sufficient to cause a disease (8).

As a result, we think that the definition and the acceptance of the patients with the diagnosis of PID by the authors is a bold claim. Clarifying these concerns will provide clearer picture to the readers.

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Competing interests: none declared.

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