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

Sirs,

I appreciate the opportunity to respond to Inan *et al*. (1) "Letter to the Editor" regarding our recent publication, "Unexpectedly high prevalence of primary immune deficiency in fibromyalgia: serologic features and clinical correlates" (2). Regrettably, this reply will emanate only from me as my long-time colleague and co-author, Dr Earl F. Winter, died shortly before the formal publication of ther article.

Inan *et al*. asks that we better identify the subtypes of primary immune deficiency (PID) seen in our FM subjects and mention that, "After IgA deficiency CVID is the most common PID in adults" (1). It should be noted, however, that while IgA deficiency is more prevalent in United States Caucasians than other types of PID (30%), IgG subclass deficiency is a close second (26%); our FM population deficiencies followed a similar pattern (3). Further, the prevalence of CVID in the USA (15%) is relatively lower than in certain European and extra-European countries (likely 22–28%) (3, 4). Additionally, as mentioned in our paper's Discussion section, we recognise that the lack of formal identification of CVID cases and longitudinal follow up of our FM cohort remain drawbacks in our study, but such a research design was beyond the scope and resources of our study. Despite these limitations, our FM subjects, as a group, did indeed report a greater history of infections [Fig. 3 in (2)], particularly sinus infections, a common feature of PID (5).

The reader may also find it of interest that during daily clinical duties we routinely find that a portion of our FM subjects fulfil CVID criteria, usually based on a clinical history of recurrent infections and demonstrable vaccine non-responsiveness. Certain of these patients require standard IVIg supplementation (1 gram/kg) for their protection; this approach, however, differs from the therapeutic use of IVIg in FM that we have described previously (2 grams/kg) (6). I also try to keep in mind that our study was not an attempt to describe all the trees in the forest, but rather to simply point out that a forest exists at all.

Inan *et al*. also asks whether any pre-existing rheumatologic or general illness might represent a hitherto underappreciated variable in assessing our subjects' clinical presentation. To this I would only point out that the clinical and serologic evaluation of the FM cohort described in our *Methods* section followed a strategy we have successfully used before (7) that excludes FM subjects with any history, "… thought to be clinically relevant, autoimmune, or chronically infectious in nature." Concomitant rheumatoid arthritis, which is usually seronegative (SNRA), was an exception because I believe, like some others, that SNRA should be viewed as a fundamentally different disease than seropositive rheumatoid arthritis (SPRA) (8); further, I also believe that SNRA may be tied to FM more intimately than has been previously appreciated.

Inan *et al*. also points out that our FM subjects' immunodeficiency might be considered secondary ID (SID) if they had any of several disorders they listed, including, "… HIV infection, lymphatic malignancies, malnutrition, renal failure, hepatic disease or hypogammaglobulinemia secondary to loss as in protein-losing enteropathy, or nephrotic syndrome or severe burns…". As we pointed out in our Methods section, and have mentioned above, none of our subjects had any of these conditions. Inan *et al*. also mention that certain drugs may induce SID; their list of drugs included the following: rituximab, glucocorticoids, carbamazepine, phenytoin, captopril, fenclofenac, sulfasalazine, penicillamine, and gold salts and antimalarial agents. All our FM subjects were originally referred for evaluation of widespread pain, and none had been previously diagnosed with, or treated for, RA; more specifically, none of our FM subjects had a history of exposure to any of these medications. Further, all immunoreactant (*i.e*. Ig and MBL) levels were determined at the subjects' original office visit, prior to any anti-rheumatic drug treatment. We do suspect that some subjects had previously undergone local "trigger point injections" with standard corticosteroid preparations by other practitioners as this is a common FM therapy in the USA. It is also possible that some had previously been exposed to captopril or another ACE inhibitor, a group of blood pressure medications that are popular in the United States. Fenclofenac, however, is not approved for use in the USA and I have been unable to identify any credible reports of the popular antirheumatic agents, hydroxychloroquine or chloroquine, causing SID. Further, none of our subjects gave a history suggestive of a typically catastrophic, hematopoietic stem cell destructive process, as might be seen in drug induced "aplastic anaemia" (9) or a more subtle drug induced hypogammaglobulinaemia (10).

I appreciate Inan *et al*.'s questions regarding IgA and IgE inclusion in our report. Recent studies have suggested a role for the distal ileum, an area of the gut protected by IgA, particularly IgA subclass 1, and IgG subclass 1, in the generation of several autoimmune diseases [reviewed in greater detail in our paper's *Discussion* section (2)] and our data demonstrated a positive correlation between serum total IgA, IgA subclass 1, and IgG subclass 1 vis-a-vis epidermal nerve fiber density (ENFD), an important peripheral marker recently described in FM (6). Additionally, IgE deficiency (we defined this as <7 IU / ml) may be used as a clue to the presence of PID, as it often accompanies that condition (11, 12). Inan *et al*. are mistaken when they dismiss mannose binding lectin (MBL) deficiency as irrelevant to our FM cohort evaluation because it is seen in "up to 5%" of the general population. As pointed out in our Table II (2) the finding of a prevalence of 25% deficiency in our cohort is unlikely to be seen through chance alone (*i.e*. differences in the prevalence of MBL deficiencies in the two populations were highly significant; p-value <0.0002). I do agree, however, and it is pointed out in our paper's Discussion section, that MBL deficiency is considered more likely to be clinically important when it is combined with other Ig deficiencies (13). None of our FM cohort subjects demonstrated isolated MBL deficiency. That is, all subjects with MBL deficiency also had another identifiable Ig deficiency [Fig. 1 in (2)].

In summary, then, I conclude that a substantial proportion of FM subjects, with or without coincident RA, have serologic and clinical evidence of PID. In our FM subject cohort these findings cannot be explained by a pre-existing medical illness, medication exposure, or other toxic or infectious environmental agent. Appreciation of this phenomenon may help in the identification of FM subjects and open new avenues into understanding FM clinical manifestations and immunopathogenesis.

X.J. Caro, *MD, FACP, FACR*

Southern California Fibromyalgia Research and Treatment Center, Northridge, CA, USA.

Please address correspondence to:
Xavier J. Caro
Director, Southern California Fibromyalgia Research & Treatment Center,
18350 Roscoe Blvd. Suite 418
Northridge, CA 91325-4174, USA.
E-mail: xjcaro@earthlink.net

Competing interests: none declared.

References

1. INAN MI, BALABAN YA: Comment on Unexpectedly high prevalence of primary immune deficiency in fibromyalgia: serologic features and clinical correlates. *Clin Exp Rheumatol* 2024; 42: 1282.
2. CARO XJ, WINTER EF: Unexpectedly high prevalence of primary immune deficiency in fibromyalgia: serologic features and clinical correlates. *Clin Exp Rheumatol* 2022; 40(6): 1076-83. https://doi.org/10.55563/clinexprheumatol/mimkj3
3. JOSHI AY, IYER VN, HAGAN JB, St SAUVER JL, BOYCE TG: Incidence and temporal trends of primary immunodeficiency: a population-based cohort study. *Mayo Clin Proc* 2009; 84: 16-22. https://doi.org/10.4065/84.1.16
4. HASSAN A, GHOLAMREZA A, SHARIFI L *et al*.: Global systematic review of primary immunodeficiency registries. *Expert Rev Clin Immunol* 2020; 16(7): 717-32.

https://doi.org/10.1080/1744666x.2020.1801422
5. McGEADY SJ, INCAUDO GA: Immunodeficiency and sinus disease. *In*: CHANG CC, INCAUDO GA, GERSHWIN (Eds.): Diseases of the Sinuses. 2nd Ed. Springer, New York, 223-46.
6. CARO XJ, WINTER EF, DUMAS AJ: A subset of fibromyalgia patients have findings suggestive of chronic inflammatory demyelinating polyneuropathy and appear to respond to IVIg. *Rheumatology* (Oxford) 2008; 47(2): 208-11. https://doi.org/10.1093/rheumatology/kem345
7. CARO XJ, WINTER EF: Evidence of abnormal epidermal nerve fiber density in fibromyalgia: clinical and immunologic implications. *Arthritis Rheumatol* 2014; 66(7): 1945-54. https://doi.org/10.1002/art.38662
8. CARBONELL-BOBADILLA N, SOTO-FAJARDO C, AMEZCUA-GUERRA LM *et al*.: Patients with seronegative rheumatoid arthritis have a different phenotype than seropositive patients: A clinical and ultrasound study. *Front Med* (Lausanne) 2022; 16: 978351. https://doi.org/10.3389/fmed.2022.978351
9. YOUNG NS: Acquired aplastic anemia. *Ann Intern Med* 2002; 136(7): 534-46. https://doi.org/10.7326/0003-4819-136-7-200204020-00011
10. KAPLAN B, BONAGURA VR: Secondary hypogammaglobulinemia: an increasingly recognized complication of treatment with immunomodulators and after solid organ transplantation. *Immunol Allergy Clin North Am* 2019; 39(1): 31-47. https://doi.org/10.1016/j.iac.2018.08.005
11. ELKUCH M, GREIFF V, BERGER CT *et al*.: Low immunoglobulin E flags two distinct types of immune dysregulation. *Clin Exp Immunol* 2017; 187(3): 345-52. https://doi.org/10.1111/cei.12885
12. MATRICARDI PM: The very low IgE producer: allergology, genetics, immunodeficiencies, and oncology. *Biomedicines* 2023; 11(5): 1378. https://doi.org/10.3390/biomedicines11051378
13. TURNER MW: The role of mannose-binding lectin in health and disease. *Mol Immunol* 2003; 40: 423-9. https://doi.org/10.1016/s0161-5890(03)00155-x