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

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Abstract

Objective

We sought laboratory evidence of primary immune deficiency (PID), a condition known to be associated with recurrent infections and autoimmunity, in fibromyalgia (FM). We correlated laboratory findings with a clinical history of recurrent infections and reduced epidermal nerve fibre density (ENFD).

Methods

We prospectively measured serum total and subclass concentrations for IgA, IgG, IgM, IgE, and mannose-binding lectin in 72 adult FM subjects (31 “FM only;” 41 “FM+RA”) and compared those results against historical controls. We also administered a novel “Lifetime History of Infections” questionnaire to all FM subjects and 40 apparently healthy, community volunteers matched for age, race, and gender. ENFD values available for 49/72 FM subjects were also correlated with immunoreactant levels.

Results

Of FM subjects, 96% (69/72) had ≥3 and 85% (61/72) had ≥4 of 9 immunoreactants below or within the lowermost quartile of historical normal values. Recurrent sinus infections occurred more often in “FM only” (p=0.06), and “FM+RA” subjects (p=0.02) than controls. “FM+RA” subjects had a significantly greater history of recurrent, severe non-sinus infections (p=0.04). The prevalence of total IgA deficiency was significantly greater in “FM only” than in “FM+RA” subjects (p=0.04). We also found a direct correlation between total IgA (p=0.02), IgA1 (p=0.005), and IgG1 (p=0.04) concentrations and ENFD in “FM only” subjects.

Conclusion

Serologic evidence of PID in FM is common and correlates with a clinical history of recurrent sinus and non-sinus infections, and reduced ENFD. This study suggests that PID may be important to diagnostic and therapeutic considerations in FM.

Key words

fibromyalgia, pain, chronic fatigue syndrome, chronic widespread pain, epidermal nerve fibre density, small fibre neuropathy, immune deficiency, primary immune deficiency, IgA, IgA subclasses, IgG, IgG subclasses, mannose-binding lectin
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Introduction
The role of primary immune deficiency (PID) in the genesis of human suffering during adulthood is much underestimated. Some aspects of this inappreciation are due to the subtlety and complexity of the immune system, while others likely reflect the better-known connection of PID with the extremes of life (1). Whatever the reasons, adult rheumatologists need to be aware of PID because of its common association with recurrent infections, autoimmunity, and neoplasia (2-5).

Herein, we present data showing that humoral immune deficiency, as evidenced by subnormal serum concentrations of certain immunoglobulin (Ig) components, a complement activating protein, mannose-binding lectin (MBL) (6), and the prevalence of a history suggestive of enhanced susceptibility to recurring infections is rather common in FM. We also discuss the implications of these findings vis-à-vis the pathogenesis and clinical presentation of FM.

Methods
Setting, clinical assessment, and FM subgroup assignment
Eighty consecutive subjects, between 18 and 90 years of age, referred during routine outpatient rheumatology, clinical practice, between January 2015 and May 2017, who met 1990 ACR diagnostic criteria for FM (7), were enrolled. All gave consent for the anonymous use of their health data; our facility’s ethics committee (IRB) approved the study. Subjects underwent comprehensive evaluation as described previously (8). No other degenerative or metabolic condition precluded inclusion in this study unless thought to be clinically relevant, autoimmune or chronically infectious in nature. Rheumatoid arthritis was an exception, leading instead to a separate analysis as a FM subject with concomitant RA (i.e. “FM+RA”).

Immunoreactant and ENFD measurements
Serum levels of IgG, and IgA subclasses, total IgE, and IgM [immunoturbidimetric (IT) method], and mannose-binding lectin (MBL) [enzyme linked immunosorbent assay (ELISA)] values were determined by our reference laboratory (LabCorp Clinical Labs, San Diego, CA, USA); results were confirmed by repeat analysis 6–9 weeks later. To define PID we used the adult lower limits of normal (LLN) and range standards suggested by Schroeder et al. (9). We estimated Quartile values for IgG, IgA, and IgM components by dividing their ranges into four equal parts (i.e. range/4 = Quartile 1-4) (10). The Ig values used to define the LLN and Q1 for IgG/A/M are listed in Figure 1. We allowed the LLN for IgE to coincide with our estimate for IgE Q1 (i.e. <7 IU/ml) as the concepts of LLN and Q1 for IgE are not well defined (11). MBL status was defined as: <50 ng/ml (deficient), >50 but <500 ng/ml (possibly deficient), and >500 ng/ml (normal). Most FM subjects also underwent a 3 mm punch skin biopsy at the distal calf for determination of epidermal nerve fibre density (ENFD) and consequent small fibre neuropathy (SFN) as previously described (8). Subsequently, we correlated immunoreactant levels and ENFD.

Assessment of prior serious infections
A brief, novel, self-administered questionnaire asked each study subject to estimate the number of infections (from 0 to ≥6) sustained during their lifetimes in the following categories: sinusitis, pneumonia, urinary tract infections, pyelonephritis, recurrent skin infections, bronchitis, intestinal infections, and otitis media. To limit overestimation, we truncated the number of each at ≥6. One of the authors (XJC) reviewed this “Lifetime History of Infections” questionnaire with each subject for clarity of understanding. A diagnosis of chronic recurrent sinusitis (CRS) was accepted only if there was a history of repeated physician prescribed antibiotic therapy, ENT subspecialty confirmation, or a corroborating sinus radiographic series or CT scan. The same questionnaire was administered to 40 apparently healthy, age (±5 years), gender and race matched community volunteers recruited from an indoor urban shopping mall approximately 5 miles from our study facility. Volunteers denied any history of rheu-

Competing interests: none declared.
matic disease, diabetes, cancer within 5 years, or known immune deficiency. Volunteers were compensated with a $5 gift card.

Statistical analysis

Immunoreactant differences between FM groups and literature controls were calculated by Chi square; FM intergroup differences for infections were by Z Test for Two Population Proportions. Three missing immunoreactant data cells were imputed using mean value substitution (12). Correlations were made by Pearson’s method. Between group comparisons for the prevalence of infections detected in FM and community controls were made using Mann Whitney U-test. Web based statistical programmes assumed a p-value ≤0.05 as significant (one tailed, unless otherwise indicated).

Results

FM subjects’ demographics

Eighty FM subjects were screened; 8 were excluded (e.g. uncontrolled diabetes mellitus, prior cancer chemotherapy, etc.). Of 72 remaining FM subjects 31 (43%) had “FM only” and 41 (57%) had concomitant RA (“FM + RA”). The “FM only” group’s mean age was 63 yrs. (range 28–72; SD ± 16); 24 (77%) were women. The “FM + RA” group’s mean age was 67 yrs. (range 23–90; SD ± 13); 37 (90%) were women. Eighty-nine percent of FM subjects were Caucasian (64% European and 25% Hispanic); 11% were of other races (Asian, American Indian, African American). Twenty-two percent of “FM + RA” subjects had IgM rheumatoid factor and 25% had CCP – IgA/G. None of the 72 FM subjects were current smokers or alcoholic.

Immunoreactant data

Immunoreactant data are enumerated in Figure 1, and Tables I and II. When our FM subjects were considered as a whole, 96% (69/72) had ≥3, and 85% (61/72) had ≥4, immunoreactant levels below the LLN or within the lowermost quartile of historical normal values. IgG Subclass 3 (58.3%; 42/72) deficiency was slightly more prevalent than IgG Subclass 1 deficiency (55.6%; 40/72). The odds ratio (OR) for a FM subject (either “FM only” or “FM + RA”) having “Any Ig” deficiency (i.e. <LLN), compared to literature-based norms, was 1.150 (95% CI: 157 - 8399). Total IgA deficiency (i.e. <LLN) was significantly more prevalent in “FM Only” (41.9%) compared to “FM+RA” (19.5%) (p=0.04) (Table II). No other significant intergroup immunoreactant differences were found.

Of FM subjects who were deficient in IgG Subclass 1, 40% were also deficient in IgG Subclass 3; this association was statistically significant in the “FM + RA” subgroup (r=0.277; p=0.04). Nineteen percent of FM subjects who were deficient in IgG Subclass 2 were also deficient in IgG Subclass 4. There was a strong association between IgG Subclass 2 and Subclass 4 concentrations (values in mg/dl) in our “FM only” subjects (r=0.671; p<0.0001), and in our 72 FM subjects taken as a whole (r=0.417; p=0.0001).

Of our 71 FM subjects whose MBL values were available for analysis, 25% (18/71) had some degree of MBL deficiency (i.e. <500 ng/ml) (7, 18). Ten percent (7/71) had a MBL level of 50-500 ng/ml, and 15 % (11/71) had unmeasurable levels (i.e. <50 ng/ml) (18). There was no significant intergroup difference in the prevalence of MBL deficiency (i.e. <500 ng/ml) in “FM only” (8/31) compared to “FM+RA” (10/41) (p=0.89).

Forty-one percent (29/71) of our FM subjects had an elevated MBL level (>1000 ng/ml). There was no significant difference in the prevalence of elevated MBL levels (i.e. >2000 ng/ml) in “FM only” (13/31 elevated) compared to “FM + RA” (16/40 elevated) subgroups (p=0.44).

When we compared all FM subjects who were ≥60 years to those ≥60 years of age there were no significant differences in Ig or Ig subclass levels (i.e. we found no correlation between Ig levels and age). We also found no significant differences in Ig levels between genders for our 72 FM subjects taken as a whole (data not shown).

Sinus and other serious infections

The number of “sinus infections” referred by our 72 FM subjects compared to normal subjects differed significantly at ≥6 total sinus infections and ≥6 “other serious infections” (i.e. not including sinus infections) (Fig. 3). This difference was significant for “FM + RA” versus apparently healthy controls’ recollection of “sinus infections” (p=0.02), and “other severe infections” (p=0.003). There was also a trend towards a significant difference in the estimation of “sinus infections” in “FM only” compared to apparently healthy controls (p=0.06). Further, the number of “other severe infections” recalled by our “FM + RA” group was significantly greater than by our “FM only” group (p=0.04).

ENFD correlates

Serum levels of total IgA, IgA subclass 1, and IgG subclass 1 correlated significantly with ENFD values in our FM subjects (Table I, Fig. 2). No other immunoreactant level correlated significantly with ENFD values.

Discussion

In 1991 Riederer became the first to describe PID in an FM subject (13). He reported a 26-year-old female suffering recurrent infections “traced back to childhood,” who presented with “classic symptoms of fibromyalgia.” His patient had rather profound IgA deficiency (total IgA = 20 mg/dl), and IgG subclass deficiencies (total IgG = 633 mg/dl; IgG subclasses 2 and 3 <10 mg/dl; IgG subclass 4 <1 mg/dl). An array of other immunologic and inflammatory markers was unremarkable, save a “low normal” number of NK cells and a “discretely degraded” CD4/CD8 ratio of 1.02. The author concluded that the “…immunopathy in the presented [FM] case [is] not coincidental…”.

More recently, Barton et al. (14) identified FM in 18.7% of 300 retrospectively surveyed adult patients referred because of recurrent/severe respiratory tract infections, or hypogammaglobulinaemia (mainly Ig subclass deficiency). Interestingly, the PID immunophenotype did not differ between their subjects with and without FM. Like Riederer (13), they found no discernable lymphocyte profile marker that distinguished PID
Fig. 1. Immunoreactant levels in 72 FM subjects (31 “FM only” [A] and 41 “FM+RA” [B]). Lower limits of normal (LLN) and ranges were those suggested for normal adults by Schroeder et al. (9). IG LLN were as follows: IgG Subclass 1 (IgG1) ≤500 mg/dL, IgG2 ≤200 mg/dL, IgG3 ≤50 mg/dL, IgG4 ≤20 mg/dL, IgA1 ≤140 mg/dL, IgA2 ≤20 mg/dL, IgM ≤25 mg/dL (18). Ig quartile 1 (Q1) values were as follows; Q1 for IgG subclass 1 (IgG1-Q1) >500-675 mg/dL, IgG2-Q1 >200-300 mg/dL, IgG3-Q1 >50-62.5 mg/dL, IgG4-Q1 >20-40 mg/dL, IgA1-Q1 >140-210 mg/dL, IgA2-Q1 >20-27.5 mg/dL, and IgM-Q1 >25-96 mg/dL (12). Ig results are stratified into those ≤ LLN (red), those falling within Q1 (yellow), and those above Q1 (i.e. Q2-4) (green). LLE for IgE was <7 IU/ml. Mannose binding lectin (MBL) was defined as deficient, ≤ 500 ng/ml (red) and normal >500 ng/ml (green) (13, 22).

*denotes “FM + RA” subjects. All Ig values are mg/dL, MBL are ng/ml and IgE are IU/ml.
Together, these two studies suggest that, in some adults, PID might be a necessary, though not sufficient, prerequisite to the development of FM. Ours is the first study to prospectively quantitate humoral immunoreactant levels in consecutive, unselected adult FM subjects, and correlate these laboratory findings with clinical evidence of recurrent infections and ENFD. Surprisingly, 96% (69/72) of our subjects were either low or frankly deficient in ≥3 of 9 immunoreactants and 85% (61/72) were either low or frankly deficient in ≥4 of 9 immunoreactants (Fig. 1, Table I and II) suggesting a rather broad spectrum of humoral immune deficiencies in FM.

<table>
<thead>
<tr>
<th>Table I. Immunoreactant characteristics of 72 adult FM subjects and their correlation with ENFD findings.</th>
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<tr>
<td><strong>Meas.</strong></td>
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<td><strong>Total</strong></td>
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Meas: measurement; IgA1, 2, IgG1..., etc.: IgA Subclass 1…, etc; MBL: mannose-binding lectin; MBL w/o: all MBL values excluding those <50 or >4000 ng/ml; ENFD: epidermal nerve fibre density; Std. Dev.: standard deviation; ENFD Correl. N: number of subjects’ ENFD values correlated with given immunoreactant (IR) value; ENFD Correl. R: Pearson r value for IR/ENFD correlation.

**Table II.** Prevalence of IR deficiency (≥2 SD below mean) in 72 adult FM subjects compared to normal population estimates.

<table>
<thead>
<tr>
<th>Immunoreactant (IR)</th>
<th>IR Deficiency in “FM Only” %</th>
<th>IR Deficiency in “FM+RA” %</th>
<th>IR Deficiency in All FM %</th>
<th>Est. Deficiency in Nml. Population %</th>
<th>“FM Only” vs. Nml. (p-value)</th>
<th>“FM+RA” vs. Nml. (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA (Total)</td>
<td>41.9% (13/31)</td>
<td>19.5% (8/41)</td>
<td>29.2% (21/72)</td>
<td>0.17% (1/600)</td>
<td>&lt;0.0002</td>
<td>&lt;0.0002</td>
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<tr>
<td>IgA1</td>
<td>41.9% (13/31)</td>
<td>29.3% (12/41)</td>
<td>34.7% (25/72)</td>
<td>0.17% (1/600)</td>
<td>&lt;0.0002</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>IgA2</td>
<td>16.1% (5/31)</td>
<td>17.1% (7/41)</td>
<td>16.7% (12/72)</td>
<td>0.17% (1/600)</td>
<td>&lt;0.0002</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>IgG1</td>
<td>54.8% (17/31)</td>
<td>56.1% (23/41)</td>
<td>55.6% (40/72)</td>
<td>0.08% (1/1200)</td>
<td>&lt;0.0002</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>IgG2</td>
<td>25.8% (8/31)</td>
<td>17.1% (7/41)</td>
<td>20.8% (15/72)</td>
<td>0.08% (1/1200)</td>
<td>&lt;0.0002</td>
<td>&lt;0.0002</td>
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<tr>
<td>IgG3</td>
<td>58.1% (18/31)</td>
<td>58.5% (24/41)</td>
<td>58.3% (42/72)</td>
<td>0.08% (1/1200)</td>
<td>&lt;0.0002</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>IgG4</td>
<td>58.1% (18/31)</td>
<td>53.7% (22/41)</td>
<td>55.6% (40/72)</td>
<td>0.08% (1/1200)</td>
<td>&lt;0.0002</td>
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</tr>
<tr>
<td>IgM</td>
<td>9.7% (3/31)</td>
<td>2.4% (1/41)</td>
<td>5.6% (4/72)</td>
<td>0.08% (1/1200)</td>
<td>&lt;0.0002</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>MBL</td>
<td>25.8% (8/31)</td>
<td>24.4% (10/41)</td>
<td>25% (18/72)</td>
<td>5 - 7%*</td>
<td>&lt;0.0002</td>
<td>&lt;0.0002</td>
</tr>
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</table>

1Prevalence of Ig deficiency in normals from Srinivasa et al. (41).
2Prevalence of MBL deficiency in normals varies geographically and ethnically; listed estimate is in European Caucasians (Super et al. 42).
3“FM Only” (n = 31); “FM+RA” (n = 41).
4“FM Only” (n = 31); “FM+RA” (n = 41).
5Mean: measurement; IgA1, 2, IgG1..., etc.: IgA Subclass 1…, etc; MBL: mannose-binding lectin; MBL w/o: all MBL values excluding those <50 or >4000 ng/ml; ENFD: epidermal nerve fibre density; Std. Dev.: standard deviation; ENFD Correl. N: number of subjects’ ENFD values correlated with given immunoreactant (IR) value; ENFD Correl. R: Pearson r value for IR/ENFD correlation.

Subjects with FM from those without. Together, these two studies suggest that, in some adults, PID might be a necessary, though not sufficient, prerequisite to the development of FM. Ours is the first study to prospectively quantitate humoral immunoreactant levels in consecutive, unselected adult FM subjects, and correlate these laboratory findings with clinical evidence of recurrent infections and ENFD. Surprisingly, 96% (69/72) of our subjects were either low or frankly deficient in ≥3 of 9 immunoreactants and 85% (61/72) were either low or frankly deficient in ≥4 of 9 immunoreactants (Fig. 1, Table I and II) suggesting a rather broad spectrum of humoral immune deficiencies in FM. Identifying laboratory evidence of humoral immunodeficiency may be chal-
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Fig. 2. Relationship between Serum IgA (Total IgA ♦ and IgA Subclass 1 □ ) and Calf ENFD in “FM Only” subjects. There was a significant direct correlation of “FM Only” subjects’ serum Total IgA (r=0.49, p=0.007) and IgA Subclass 1 (r=0.58, p=0.004) with ENFD. The equation of the trend line (y=mx + b, where m=slope, and b=y value when x=0) for Total IgA=14 (ENFD) + 127.5; for IgA Subclass 1=12.7 (ENFD) + 91.1. ENFD=epidermal nerve fibre density, IgA1=IgA Subclass 1.

Fig. 3. Prevalence of severe infections recalled by 72 FM subjects compared to 40 healthy controls subjects. “FM only” subjects (n=31); “FM + RA” subjects (n=41).

A) depicts recall of only “sinus infections” amongst FM and control subjects.
B) depicts recall of “other severe infections” (excluding sinus infections) amongst FM and control subjects. All p-values are calculated at ≥6 infections reported.

lenging, due to the absence of agreed upon normal reference intervals (RI) for these immunoproteins (15). Older, “direct sampling” methods of establishing immunoreactants’ RI in large cohorts of volunteers are difficult and expensive for modern laboratories or clinical investigators to reproduce de novo today.

Newer, statistically based methods of generating laboratory RI, pioneered by Hoffman (15) and others, have become popular but depend on the “fact that most of the patient specimens sent to laboratories for analysis are normal” (15). These mathematically derived RI reflect the reference laboratory’s experience with “normal” immunoreactant values established using cumulative testing data generated from thousands of clinical samples. It is rare, however, for clinicians to order quantitative immunoprotein concentrations as a part of their evaluation of asymptomatic patients, rendering this RI approach vulnerable to a systematic measurement error reflecting the bimodal distribution of oft tested patient groups surveyed for these immunoreactants, i.e. those suspected of having unusually low or unusually high values.(16)

We avoided these issues by relying on a traditional “direct observation” RI set found in a well-respected and readily available textbook of immunology (9), and investigated its clinical relevance vis-à-vis any history of recurring infections and ENFD in FM.

Population studies show that Ig subclass concentrations are genetically determined, generally follow a log-normal distribution, reach adult levels by mid-adolescence, and – absent a significant stressor – remain relatively fixed throughout the individual’s adult life (17-21). Further, the occurrence of a particularly high or low Ig class or subclass concentration tends to co-travel with other similarly high or low immunoreactant levels (22). Several studies have also suggested that there may be minor differences in serum Ig concentrations associated with advancing age, gender, race, smoking, and alcohol use (18, 23, 24). None of these factors were important to our subjects’ immunoreactant findings.

Our study populations were relatively homogenous and made up mainly of women, none of whom were smokers or alcoholic. When we compared FM subjects who were <60 years of age to those ≥60 years of age we found no correlation between Ig levels and age. We also found no significant differences in immunoreactant levels between genders for our 72 FM subjects taken as a whole, or when analysed as subgroups (data not shown). Even though some of our FM subjects might have qualified as having had common variable immune deficiency (CVID), none had the wide swings in Ig levels occasionally associated with this disorder (25).

Individuals whose Ig concentrations fall below the LLN or within Q1 are known to suffer more frequent and more severe bacterial and viral infections than those whose Ig values fall above those levels (26). For that reason, we conducted a questionnaire-based survey of our 72 FM subjects, and 40 apparently healthy community controls, using a novel “Lifetime History of Infections” questionnaire, which broadly surveyed participants’ history of significant sinopulmonary, cutaneous, gastrointestinal, and urinary tract infections. We analysed our subjects’ responses in two broad categories, i.e. sinus related, and other, serious but non-sinus related infections.

We chose to emphasise symptoms of CRS in our questionnaire because of its well-known association with PID (27). As depicted in Figure 3, we found that “FM + RA” subjects gave a history of significantly more sinus (p=0.04) and non-sinus infections (p=0.002) than...
control subjects. Our “FM only” subjects claimed significantly more non-sinus infections \( p=0.05 \) and tended toward a history of more sinus infections \( p=0.06 \) than controls. We truncated sinus infection estimates at a maximum of ≥6 infections though many FM subjects, recalled dozens of sinus infections over their lifetime. The prevalence of ≥6 sinus infections recalled by controls (15%) is a figure agreeing well with U.S. national surveys for chronic rhinosinusitis, but higher than reported in Olmsted County, MN, USA. (28).

Eighteen of 72 (25%) of our FM subjects had evidence of MBL deficiency \((i.e., \text{MBL levels }<500 \text{ ng/ml})\) presumably representing an admixture of subjects heterozygous \((>50 \text{ but } <500 \text{ ng/ml})\) and homozygous \((<50 \text{ ng/ml})\) for one or more missense allele substitutions leading to MBL deficiency (6, 29). There was no significant difference in the prevalence of MBL deficiency or elevation, however, between our “FM only” and “FM + RA” groups. Isolated MBL deficiency is commonly thought to be clinically silent due to naturally occurring immunological redundancy, while MBL deficiency combined with other forms of immune dysfunction, such as our FM subjects’ IgG subclass deficiency, is thought to be more clinically relevant (29).

We doubt that any of our subjects had idiopathic “late-onset immunoglobulin deficiency” \((\text{LOID})\) as described by Hermans et al. (30). Their subjects were, on average, younger than ours \((\text{LOID mean age } 30.7 \text{ yrs. } \text{vs. } \text{ “FM only” and “FM + RA” mean age } 63 \text{ and } 67 \text{ yrs.}, \text{respectively})\). Their subjects also had a high prevalence of sinusopulmonary disease, but 28% had frank bronchiectasis, and 28% had splenomegaly. Steatorrhea, cholelithiasis, and nodular lymphoid hyperplasia of the small bowel were also frequent in their LOID subjects. Furthermore, 24% of their 50 subjects developed some form of neoplasia \((\text{mainly gastric carcinoma or lymphoreticular malignancies})\). Some also had “arthritis,” but none had FM. None of our FM subjects manifested any of these serious complications of their PID, at least within the context of our study time frame. All in all, we do not consider the clinical features of LOID as fitting our subjects’ FM clinical phenotype.

The finding of PID in FM predicts other known features of immune dysfunction, such as autoimmunity and neoplastic disease (2-5). This idea might be supported in FM by recent descriptions of associated small and large fibre neuropathic injuries, with their known connections to immune dysfunction (8, 31, 32), and the greater than expected prevalence of autoimmune disorders noted in Barton et al. FM-PID cohort (14). A greater than expected proclivity to a variety of malignancies, including female breast, prostate, lung, and colonic cancer in FM has also been suggested (33). Interestingly, our “FM only” subjects demonstrated a significant, positive correlation between IgA \((\text{both total IgA and IgA subclass 1})\) and IgG subclass 1 levels and the ENFD findings associated with a SFN \((\text{Table I, Fig. 1})\). It is known that the protective effects of non-complement fixing IgA, particularly IgA Subclass 1 \((\text{augmented by IgG subclass 1, 2 and 3, IgM, and IgD})\), are amongst the most active local agents guarding against bacterial and other microbiota related pathogens in the gastrointestinal system, particularly from the nasopharyngeal area to the distal ileum (34-36). It is tempting to speculate that a disruption of regional gastrointestinal homeostasis contributes to the ingress and systemic spread of noxious and antigenic substances in FM resulting in direct or indirect peripheral nervous system injury \((\text{PNS})\) and autoimmunity (8, 32).

It is also biologically plausible that such a peripheral SFN, principally involving nociceptive C-fibres, along with peripheral large fibre pathology (31, 32), serve as unmitting “pain drivers” in FM. These could help to explain the phenomena of spinal cord wind up and CNS sensitisation \((i.e. \text{“central sensitisation”})\) so frequently postulated to be active in FM (37). Further, it would predict amelioration of the FM painful state with substances, such as IVIg, directed against small and large PNS structural and functional lesions (38). Nevertheless, in our experience, other coincident, painful nociceptive generators, both mechanical and inflammatory, need to be addressed for successful treatment of FM; thus, the importance of recognising concurrent autoimmune disorders such as the RA seen in our “FM+RA” subjects.

Our study has certain inherent limitations. We doubt, however, that significant misclassification error \((i.e. \text{“recall bias”})\) for recollection of infections in our FM subjects is one of them (39). None of our FM subjects had a prior PID diagnosis, knew of our interest in PID, or had been referred for investigation of possible PID. We were also careful to shuffle our novel “Lifetime History of Infections” questionnaire in amongst routine FM intake paperwork. This brief questionnaire asked for a quantitative approximation, on a 7-point numerical scale \((0 \text{ to } \geq 6)\), of the number of serious infections of 8 types \((e.g. \text{sinusitis, pneumonia, etc.})\) previously experienced. Infections recalled were truncated at ≥6 to limit overestimation, though many of our FM subjects gave a history of dozens of infections, particularly sinus infections.

Evaluation of 23-valent pneumococcal vaccination responses in our FM subjects might have better established FM immune deficiency (40). Family studies and longitudinal follow-up of the present subjects would also have been of interest. Both of these strategies, however, were beyond the scope of this study.

We have, then, herein described a substantial cohort of unselected, adult FM subjects, with and without features of RA, who had laboratory evidence of significant immunoreactive insufficiencies. In the main, these consisted of IgG subclass, IgA subclass, and MBL deficiencies. These deficiencies were associated with a significantly greater estimation of previous sinus and non-sinus infections amongst FM subjects than apparently healthy controls, suggesting that this phenomenon may be associated with clinically important translational propensities to infectious disease in FM. There was also a noteworthy correlation of IgA and IgG subclass 1 levels with ENFD. Taken as a whole, our findings suggest that a better understanding of FM may require a deeper appreciation of the immunologic milieu from which it arises.
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This study is dedicated to J, M, & C.

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