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CASE STUDY

Elevation of *Candida* IgG Antibodies in Patients with Medically Unexplained Symptoms

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ABSTRACT

Background: The hypothesis that an immunologic reaction to *Candida* yeasts, present in the gastrointestinal tract, causes a diffuse collection of multisystem symptoms is not generally accepted within conventional medicine. A questionnaire, the Fungus Related Disease Questionnaire (FRDQ-7), was previously developed and used to identify patients for a randomized, placebo-controlled trial of the nonabsorbed antifungal drug nystatin. Nystatin was superior to placebo in relieving these symptoms. This provides some support for the hypotheses that underpin the "*Candida* syndrome".

Aim: The aim of this study was to identify a population with a high (>9) FRDQ-7 score and symptom-free controls and, subsequently, to explore the relationship between FRDQ-7 scores and *Candida* immunoglobulin (Ig)A, IgG, and IgM levels.

Design: This was a case-controlled study.

Methods: Santelmann has suggested that the FRDQ-7 describes people with *Candida* syndrome if the FRDQ-7 score is >9; 35 patients with medically unexplained symptoms, between ages 18 and 64, were selected for the study if they scored >9 on the FRDQ-7 questionnaire. Serum *Candida* IgA, IgG, and IgM measurements were undertaken both for this group and a group of 45 healthy age- and gender-matched controls, and the Ig concentrations were compared.

Results: *Candida* IgG concentration was significantly higher in the noncontrol group than in the control group ($p < 0.001$). No significant difference was found for *Candida* IgA or IgM concentrations.

Conclusions: Further studies are required to identify whether there is a causal link for the elevation of serum IgG found in this subgroup of patients with increased FRDQ-7 scores, or whether these two observations are parallel manifestations of a common underlying disorder.

INTRODUCTION

Medically unexplained symptoms account for approximately 20% of primary care consultations and 10% of secondary care referrals.[1] Typical symptom clusters include headaches, poor concentration, upper respiratory symptoms, gastrointestinal (GI) distress, muscle pain, joint pain, and urogenital symptoms. Such symptom clusters do not readily fit any organ-based disease group and cannot be explained by conventional medical modeling, nor do they have an agreed-upon conventional medical diagnosis.

Immunologic reaction to *Candida albicans* has been pro-

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posed as an explanation for a small subgroup of these polysymptomatic patients[2]; it has been called the "*Candida* syndrome" and was originally described by Truss.[3] There is no diagnostic test for the *Candida* syndrome, and its validity as a nosologic entity is based on the therapeutic response to targeted treatment. In an open study of 380 undiagnosed polysymptomatic subjects, Santelmann et al.[4] compared the effect of diet and antifungal treatment with the responses to an initial 70-item questionnaire derived from Crook's original work.[5] Santelman et al. then used a discrimination analysis to identify seven questions that were the most strongly predictive of treatment response and named this questionnaire the Fungus Related Disease Questionnaire (FRDQ-7).[5] Answers to each question can be scored from 1 to 3, depending on the severity of symptoms, giving a total possible score of 21. Adding the responses from these seven questions within the open study, Santelmann et al.[4] suggested that, from a pool of patients with medically unexplained symptoms, a score of >9 is predictive of an antifungal treatment response and therefore the FRDQ-7 is capable of identifying patients with *Candida* syndrome. The FRDQ-7 was then used as the recruitment instrument in a randomized placebo-controlled population-based study. One hundred and sixteen (116) suitable controls, each with an FRDQ-7 score of >9, were selected from a total of 660 persons who completed the questionnaire. The subjects were randomized to receive the nonabsorbed antifungal drug, nystatin, or an identical placebo, three times a day for a 4-week period. Patients who received nystatin treatment, irrespective of diet, experienced a significantly greater reduction in overall symptom score than those who had received placebo ($p < 0.003$).[4]

Our aim in conducting this small case-controlled pilot study was to investigate whether there is a relationship between serum *Candida* immunoglobulin (Ig)A, IgG, and IgM antibody concentrations in a population of patients with these medically unexplained symptoms identified by FRDQ-7. We wished to investigate whether this test might be a useful diagnostic aid.

METHODS

Successive patients attending a variety of medical clinics were selected if full clinical assessments, together with the results of any investigations, indicated that no definitive conventional diagnosis was present. In accordance with Santelmann et al.'s original suggestions,[4] these patients were included if they were between ages 18 and 64 or if the patients presented with two or more of the following symptoms: fatigue; headaches; poor concentration; GI distress; muscle pain; joint pain; or urogenital symptoms. These subjects then completed a modified FRDQ-7 questionnaire* and were en-

*With the approval of Dr. Santelmann, minor changes to the wording of the original (Norwegian) FRDQ-7 have been made to resolve small ambiguities. In addition, question 2 has been amended by the addition of an alternative question. In the new version (modified FRDQ-7), a history of *either* four or more antibiotic courses within a 12-month period *or* a single antibiotic course lasting a month or more now attracts a score of 3. The modified FRDQ-7 now reflects more accurately the outcome of the discrimination analysis.

Table 1. Modified FRDQ-7 Questionnaire

	Score
1. Have you at any time in your life taken a course of antibiotics?	3
2. Have you at an time in your life either: taken antibiotics continuously for a month or more *or* taken four or more courses of antibiotics within 12 months?	3
3. Do you have any symptoms that worsen on damp or muggy days or in moldy places (damp rooms, public buildings, greenhouses, etc.)?	3
4. Do you crave sugar and sweetened or sugary foods?	3
5. Do you experience the feeling of being drained (exhausted without obvious cause)? If so, does this happen:	
occasionally or mildly?	1
frequently or moderately severely?	2
severely (disabling)?	3
6. *Female*—Does vagina burning, itching, or discharge bother you? *Male*—Does penis burning, itching, or discharge bother you? If so does this happen:	
occasionally or mildly?	1
frequently or moderately severely?	2
severely (disabling)?	3
7. Are you bothered by burning, itchy, or watery eyes? If so does this happen:	
occasionally or mildly?	1
frequently or moderately severely?	2
severely (disabling)?	3

FRDQ-7, Fungus Related Disease Questionnaire.

Table 2. Summary of Baseline Demographics

	Subjects (n = *35*)	*Controls* (n = *45*)	
Males	7 (20%)	12 (27%)	ns
Females	28 (80%)	33 (73%)	ns
Mean age, yrs (range)	42.0 (16–74)	37.0 (20–64)	ns
Median FRDQ-7 (range)	13 (10–18)	6 (1–15)	$p < 0.001$

FRDQ-7, Fungus Related Disease Questionnaire; ns, not significant.

tered into the study if they had a score >9 (Table 1). Healthy age- and gender-matched controls were also recruited and all completed the same questionnaire, although their scores did not affect selection. The Southampton and South West Hampshire Research Ethics Committee approved the study (REC:05/Q1702/108).

Blood samples were obtained from each participant and the serum was incubated with *C. albicans* antigens (human isolate of *C. albicans* NCPF3310 serotype A from the National Collection of Type Cultures, Colindale, U.K.). In three separate tests, rabbit antihuman IgA, IgG, and IgM conjugated to horseradish peroxidase were then added to bind surface immobilized antibodies. After washing to remove unbound conjugate the enzyme substrate, tetra-methylbenzidine, was added to induce color development in order to demonstrate antibody binding. We used a stop solution to terminate the reaction and assessed antibody activity by a measurement of optical density against a 6-point calibration curve.

No power calculations were carried out for this exploratory pilot study. Serum IgA, IgG, and IgM concentrations were compared between groups using the Mann–Whitney *U*-Test, and the Spearman Rank correlation was used to investigate the relationship between the FRDQ-7 score and *Candida* IgA, IgG, and IgM concentrations. A logistic regression analysis was used to investigate the power of the serum concentrations to discriminate between the groups.

RESULTS

Thirty-five (35) subjects were identified who scored >9 on the FRDQ-7 (Table 2). We recruited these patients from several sources, so we are unable to identify the number approached initially. However, we are aware from previous unpublished pilot work that approximately 40% of new patients ($n = 150$) presenting with irritable bowel syndrome to a London, UK, teaching hospital score >9 on the FRDQ-7, thus providing some estimate of the possible prevalence of this condition.[†] Forty-five (45) healthy controls were also recruited. There were no significant differences in age and gender between the groups although, as expected, there was a significant ($p < 0.001$) difference in FRDQ-7 score.

Candida IgG concentration was significantly higher in the noncontrol group than in the control group ($p < 0.001$; Fig. 1). No significant difference was found when we compared the groups for *Candida* IgA or IgM concentrations.

There was a small positive, nonsignificant correlation between *Candida* IgG concentration and FRDQ-7 score (r = 0.16; $p = 0.35$) in the noncontrol group, although no such relationship was found for the control group (Fig. 2). No such correlation was evident with either *Candida* IgA or IgM concentrations.

We undertook further analyses as an indication of the predictive power of IgG to discriminate between FRDQ-7–positive subjects and healthy controls. A logistic analysis gave a significant odds-ratio of 1.09 ($p = 0.02$) for IgG with a sensitivity (probability of correctly classifying a subject) of 37% and a specificity (probability of correctly classifying a healthy control) of 82%, a positive predictive value (proportion of those classified as subjects who were subjects) of 62%, and a negative predictive value (proportion of those classified as health controls who were healthy controls) of 63%, with an overall correct rate of prediction of 62.5%.

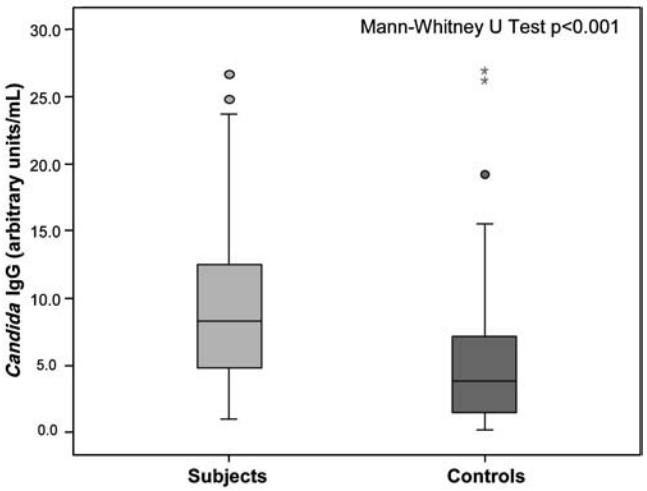

FIG. 1. Difference in mean *Candida* immunoglobulin G between noncontrol and control groups.

[†]Original work with Ingvar provides an estimate of prevalence.

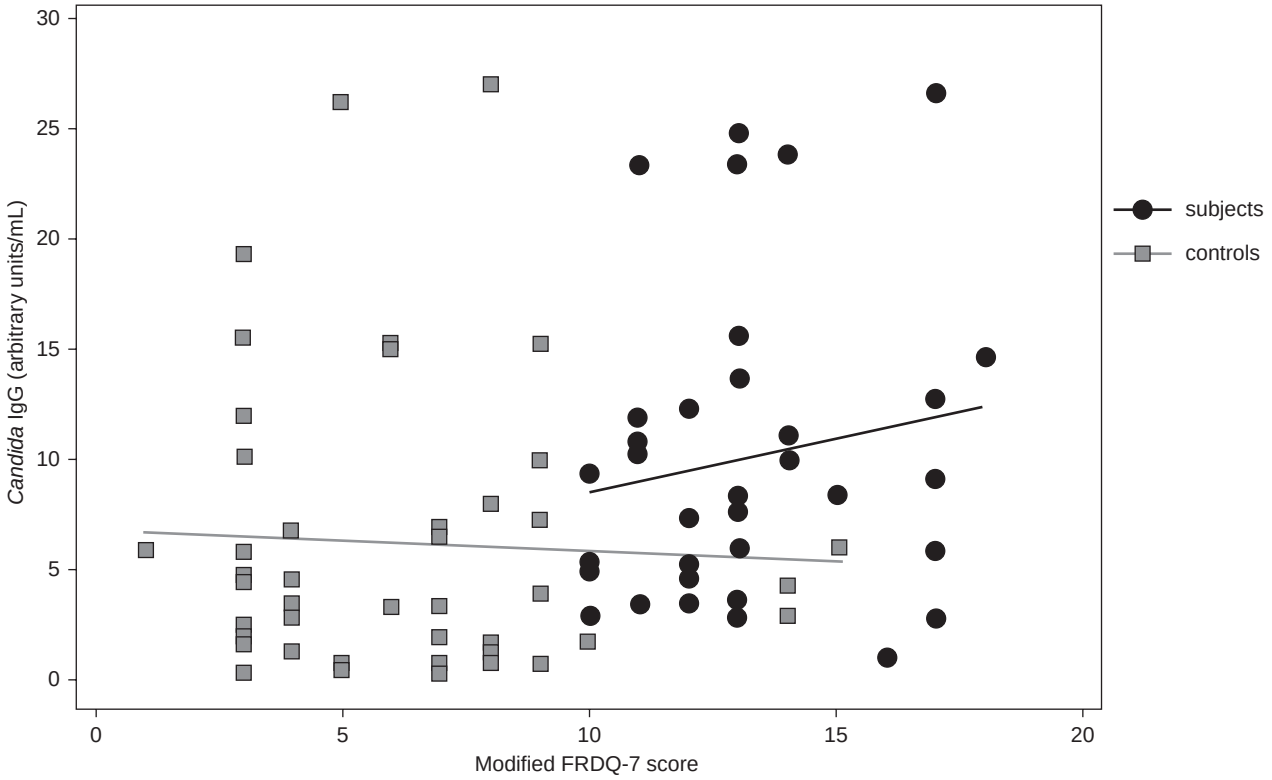

FIG. 2. Scatterplot of mean *Candida* immunoglobulin G against Fungus Related Disease Questionnaire showing separate regression lines for noncontrol and control groups.

Figure 3 shows that the receiver operating characteristic curve corresponding to this logistic analysis has an area under the curve value of 0.71, indicating relatively weak discrimination.

CONCLUSIONS

This preliminary study demonstrates a link between *Candida* IgG levels and symptom expression in polysymptomatic patients who score highly on the FRDQ-7. It also investigates whether *Candida* IgG can be used as a simple test that might help identify the polysymptomatic patients who would respond to antifungal treatment. When considering whether the test might be of diagnostic value, we found an overlap in the sensitivity and specificity of this investigation sufficient to make a reasonable discrimination between the two populations impossible.

The sensitivity and specificity analyses conclude that *Candida* IgG would identify healthy controls 82% of the time but potential antifungal responders only 37% of the time. It may be that these two populations are within the spectrum of "normality," but in any event such a test would be insufficiently discriminating to be of substantial clinical value. However, this interpretation overlooks the major limitation of our study. We did not undertake a randomized trial of antifungal treatment, and so the ideal method of subject selection–response to antifungal treatment was not available to us as a definitive diagnosis against which to correlate the proposed "diagnostic" investigation. A further study is required to evaluate *Can-*

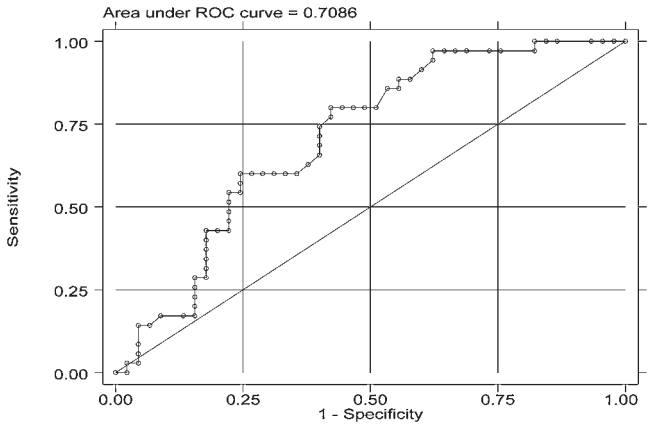

FIG. 3. Receiver operating characteristic curve of sensitivity against 1 − specificity with area under the curve of 0.7086.

dida IgG as a diagnostic test, in the context of a therapeutic double blinded placebo-controlled trial of antifungal treatment, in this group of patients.

REFERENCES

1. Kroenke K. Patients presenting with somatic complaints: Epidemiology, psychiatric co-morbidity and management. Int J Methods Psychiatr Res 2003;12:34–43.
2. Santelmann H, Howard JM. Yeast metabolic products, yeast antigens and yeasts as possible triggers for irritable bowel syndrome. Eur J Gastroenterol Hepatol 2005;17:21–26.
3. Truss CO. The Missing Diagnosis. Birmingham, AL: 1982.
4. Santelmann H, Laerum E, Roennevig J, Fagertun HE. Effectiveness of nystatin in polysymptomatic patients: A randomized, double-blind trial with nystatin versus placebo in general practice. Fam Pract 2001;18:258–265.
5. Crook WG. The Yeast Connection. Jackson, TN: Professional Books, 1983.

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