The Determination Of The Prevalence Of Undiagnosed Celiac Sprue In A Population Of Non Hodgkin's Lymphoma Patients

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A. Study Purpose

Celiac sprue is a disorder characterized by the symptoms of malabsorption and an abnormal small bowel histology, which is due to the patient's intolerance to gluten. Gluten is a protein found in wheat and wheat products. The typical symptoms of malabsorption include weight loss, abdominal distention, bloating, diarrhea and steatorrhea. However, the severity of the disease varies greatly among the celiac sprue patients. For example, a patient may have the typical small bowel histological changes, consistent with celiac sprue, but may be asymptomatic, may have iron deficiency anemia without a source of bleeding or have a metabolic bone disease without the symptoms of malabsorption. The histological changes seen in celiac sprue are the blunting and flattening of the small bowel villi along with crypt hyperplasia. These changes are nonspecific and can be seen in tropical sprue, viral gastroenteritis and severe intestinal bacterial overgrowth. However, the diagnosis of celiac sprue is established when there is clinical, biochemical and histological improvement after the commencement of a gluten free diet. Celiac sprue has been considered a disease that largely occurs in Caucasian populations.

Furthermore, celiac sprue is a fairly common disease in Northern Europe, Italy and among Ashkenazi Jews, where serological screening tests have reported the prevalence to be 1 in 250 to 3)00 of the general population. (1,2) One study in Northern Ireland reported an even greater prevalence of 1 in 122(3). In contrast, celiac sprue in the U. S. is considered to be a rare occurrence, an orphan disease. However, a recent study in Baltimore evaluating the blood donor pool reported a similar prevalence of celiac sprue in the U.S. in agreement with the European studies.(4) Possibly, the lack of recognition of celiac sprue in the U.S. is due to many celiac sprue patients being asymptomatic, having latent or silent disease.

The screening tests for celiac sprue are serological assays for antighadin antibody and antiendomysial antibody. The antighadin antibody is the antibody to gliadin peptides. Gliadin is the alcohol soluble fraction of gluten. In celiac sprue patients, gliadin peptides are toxic and induce the characteristic small bowel lesions. Both antighadin IgG and IgA antibodies are present in the serum of celiac sprue patients unless the patient is IgA deficient. The IgA antibody is a dimer and is secreted into the lumen of the small bowel. Thus, the presence of the antighadin IgA antibody in untreated celiac sprue patients is more specific but less sensitive than the IgG antibody. The sensitivity of the antighadin IgA antibody ranges from 55-85% as compared to 65-95% for the antighadin IgG antibody. In contrast, the specificity for the antighadin IgA antibody is 80- 100% as compared to 60-100% for the antighadin IgG antibody(5). The antiendomysial antibody is directed against the smooth muscle cells of the primate GI tract. Why this antibody is present in celiac sprue patients is unclear, however most likely its due to an epiphenomena. Surprisingly, there is nearly 100% specificity with the antiendomysial IgA antibody and a sensitivity of 89- 100%(5). The only antiendomysial antibody tested for is IgA, whose positivity and titer level correlates with the severity of the small bowel lesion. These serological tests besides being used to screen populations to determine the prevalence of celiac sprue, can be used to monitor compliance with a gluten free diet. If there is strict adherence to the diet, the antibody titers will normalize. Also, these screening tests can determine candidacy for a jejunal biopsy. This is important, since it is still necessary to identify the histological changes consistent with celiac sprue, before committing a patient to a lifetime on a gluten free diet.

There have been many studies revealing a higher than expected incidence of malignancy in celiac sprue patients.(6-10) However, only certain types of malignancy have been shown to have an increased

incidence, such as Non Hodgkin's Lymphoma (NHL), mostly a T-cell intestinal lymphoma, also called enteropathy associated T-cell lymphoma (EATCL), small intestinal adenocarcinoma, oropharyngeal and esophageal squamous cell carcinoma .(6,7,10). The overall lifelong risk of malignancy in celiac sprue patients has been reported to be between 8.1 and 13.3% and the risk for NHL is 4.3-9.6%(11). There is some evidence which suggests that the overall mortality rate in adult celiac sprue patients is increased from 1.9 to 4.1 fold(6,8,12). Much of the increase in mortality was due to NHL and esophageal cancer. In contrast, one study revealed the survival rate of celiac sprue patients which did not differ from the general population(13). However, 83% of these patients strictly adhered to a gluten free diet. This may explain the favorable outcome. Another study revealed adult celiac sprue patients strictly adhering to gluten free diet 6 for more than five years did not have increased incidence of malignancy(6). Both studies suggested that a gluten free diet has a protective effect against malignancy.

Some of the studies, evaluating celiac sprue and NHL, followed celiac sprue patients over time to see if they developed NHL(6,7,9,10). Most of the other studies retrospectively evaluated celiac sprue patients with NHL(1 1, 14,15). These studies revealed not all of the celiac sprue patients who developed NHL, presented with the typical presentation of intestinal lymphoma accompanied by increased abdominal pain, weight loss and malabsorption. In addition, not all NUL cases were Tcell but also were different forms of B-cell lymphoma. On average, 65% of the celiac sprue patients with NHL had the diagnosis of celiac disease for eight years before the diagnosis of lymphoma. In 20% of these patients, the diagnosis of both diseases were made simultaneously. The remaining 15% of the patients had the diagnosis of celiac sprue made up to 15 years after the diagnosis of lymphoma(11). The survival rate for most celiac sprue associated NHL is low, less than a 10% 5 year survival rate(7). One study shown most of the long term survivors did not have the previous diagnosis of Celiac sprue and thus had not been on a gluten free diet prior to the diagnosis of NHL(14). This study implied a gluten free diet has a protective effect against malignancy. Finally, there has been only one study that evaluated NHL patients looking for a subsequent diagnosis of celiac sprue and starting them on gluten free diet(16). The study revealed that the subsequently diagnosed celiac sprue patients were fully responsive to a gluten free diet. This study felt that the relationship of NHL and celiac sprue in North America was underappreciated and recommended screening test for celiac sprue in newly diagnosed NHL patients. A recent article, recommended conducting a trial of strict gluten free diet in conjunction with chemotherapy for lymphoma patients who were investigated and subsequently found to have celiac sprue(17). Thus, the purpose of this study is to determine the prevalence of undiagnosed celiac sprue in NHL patients and to start them on a gluten free diet.

B. Study Design

The aim of this study is twofold. First, to screen a population of NHL patients, preferably before chemotherapy is started, for the presence of antighadin and antiendomysial antibody in order to determine the prevalence of undiagnosed celiac sprue in this population. The belief, being that there is a high prevalence of NHL patients with undiagnosed celiac sprue. Second, the study will screen the blood donor pool for the antighadin and antiendomysial antibodies. The patients in the blood donor pool will be matched on basis of age, gender and ethnicity. The goal is to determine the prevalence of celiac sprue in the general population and to see if this result favorably compares to previous studies.

In order to determine the prevalence of celiac sprue in both populations, there will be the one time procurement of 5 cc of blood for the serological testing. For antiendomysial antibody, the test is an ELISA test, which is positive at certain dilution. In contrast, antighadin antibody titers are compared to normal values, where a titer level greater than a certain cutoff value is considered positive. Then the analysis of the serological testing to determine prevalence will use either chi-square test or Fisher exact test, depending on the number of patients determined to have celiac sprue. The chi-square will use a standard 2x2 table, comparing NHL patients and controls with their serological screening test results.

C. Study Subjects

To determine the sample size, an educated guess of the prevalence of undiagnosed celiac sprue in NHL patients was determined to be 5%. This number was determined based on the assumption that since the incidence of NHL, over the past three decades, has increased by 150%, which was not exclusively due to the HIV virus and quite possibly due to celiac sprue. Based on this assumption and the prevalence of celiac sprue in the general population to be 1 in 250, the sample size was determined to 250.

The 250 patients with NHL, will be adult patients, who currently are not on any immunosuppressive therapy, that would falsely negate antighadin and antiendomysial. antibody titers. Also, the NHL patients would not have the diagnosis of celiac sprue. The patients would be patients seen in CPMC oncology clinic, CPMC private oncologist offices and radiation therapy offices. The 250 blood donor patients will be matched on basis of sex, gender and ethnicity.

D. Recruitment Method

The patient will be approached by the oncologist in their office to determine if the patient desires to be in the study. The controls from the blood donor pool will either be approached at the time of donation or if 5 cc of blood could be taken from blood already donated and to be discarded.

E. Study Procedures

The only procedure is the noninvasive procurement of 5 cc of blood from the NHL patients. Preferably, blood will be drawn at the same time the patient was to scheduled to have blood drawn for other tests, particularly a CBC with a differential. Thus, the patient could be evaluated for relative lymphopenia, which would excluded them from the study.

F. Issues

None

G. Study Drugs

None

H. Study Questionnaire

The only questionnaire that would be filled out would be by the oncologist on confidential basis. The questionnaire would provide the age, gender, ethnicity of the patient but not their name. Also, provided would be the type of NHL, year diagnosed and presenting symptoms.

I. Confidentiality

The names of the NHL patients and controls will be strictly confidential. The patients will be allowed access to their serological screening test results.

J. Risks and Benefits

The only risk involved in this study is a non-invasive procurement of 5cc. of blood. The benefit is NBL patients could possibly be diagnosed with celiac disease and be treated appropriately with a gluten free diet.

K. Alternative Therapies

None

L. Compensation

None

M. Minors

Minor NBL patients will not be enrolled in this study.

N. Radiation or Radioactive Substances

Not applicable

O. References

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Sample Size Determination

P1= prevalence of celiac sprue in the general population = 1/250 =.004
P2= expect prevalence of undiagnosed celiac sprue in NHL population = 1/20 =.05

Formula =8 x (P, + PY(P1 - P2)2 + 2/(Pj - P2)

= 8 x (004 +.05)/(.004 -.05)2 + 2/(.004 -.05)

= 250

Assuming, Alpha =.05
Beta = .20
Power = I -Beta = .80
To have statistical significance;

Controls with celiac sprue (you need)	NHL patients with celiac sprue
0	5 (2% of 250)
1	15(6%)
2	17(7%)

Serological Screening

If antiendomysial IgA antibody is positive	The patient is assumed to have celiac sprue, then refer to a gastroenterologist
If antighadin IgA antibody is positive	The patient is assumed to have celiac sprue, then refer to a gastroenterologist
If antighadin IgG antibody is positive and antighadin IgA antibody is also positive	The patient is assumed to have celiac sprue, then refer to a gastroenterologist
If antighadin IgG antibody is positive but antighadin IgA antibody is negative	Then screen the patient for IgA deficiency: if IgA deficient, patient is assumed to have celiac sprue. If not IgA deficient, patient does not have celiac sprue.