

Celiac Disease

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Abstract 321148: Is celiac disease different in the elderly compared to the young?

This is an interesting and provocative study from the group in New York. It is a retrospective analysis of a little more than one thousand patients in their database. They divided them into patients diagnosed over age 65 (N=125) and those diagnosed between ages 18-30 (N=149) and looked at differences in clinical presentation, duration of symptoms, intestinal damage, and other co-morbid illnesses such as autoimmune diseases. There was a predominance of females over males, more so in the younger group (1:3.9 in the younger group vs. older group 1:1.3). There was no difference in the clinical presentation between the two groups or in the duration of symptoms prior to the diagnosis. The average duration between the onset of symptoms and the diagnosis was 6 years, regardless of the group. Diarrhea was more prevalent in males in the older group. There was a higher prevalence of thyroid disease (14 v 7%) and neuropathy (11 v 4%) in the older population.

These subtle differences in presentation are difficult to explain and clearly require further study. Why people present early versus late in life is at present not clear, nor is the reason for the increase in thyroid disease and neuropathy. Perhaps the time of gluten exposure is important, however no definitive data are available at the moment to support this hypothesis.

Abstract 318695: Prevalence of human anti-transglutaminase antibodies (H-TGA) in patients with unexplained infertility and infertility with a known cause.

The authors assessed the prevalence of H-TGA in a large number of patients with infertility. They evaluated 86 patients with unexplained infertility (43 males and 43 females) and 376 (240 males and 136 females) with infertility of known cause. They did serological testing with a TTG and in those that tested positive, recommended biopsy to confirm the diagnosis. Overall, six out of 462 people were TTG positive. They biopsied three of six and all had classical biopsy damage typical of celiac disease. Two out of 86 with unexplained infertility (2.3%) had celiac disease; a little more than twice the expected prevalence. On the other hand, the prevalence in those with recognized causes of infertility was equal to the expected in the general population. So, if you have unexplained infertility, the prevalence of celiac disease is higher than expected. The question is, "When does increased prevalence justify general screening for that risk group?" In other words, is it more cost effective to screen all people with unexplained infertility or is there another cut off that makes this cost effective? The other thing that is interesting to me is the difference divided by gender. In males with unexplained infertility, the prevalence goes up to 4.6%. No women were identified with celiac disease among the group with unexplained infertility. Of those with known causes of infertility, only 0.4% of males were TTG positive while three

out of 136 (2.2%) women were TTG positive. If we look only at gender, there is an eight-fold increase in males with unexplained infertility who may have celiac disease.

The take home message from this study for me is that if you are a male with unexplained infertility, you've got to be screened. If you are a female, what are you going to do? There are many studies before this one that describe an increased prevalence of celiac disease in unexplained infertility in females. In fact, the recommendation is to screen them, but this study seems to contradict that, but again we are talking about small numbers here. I think this was an intriguing abstract.

Abstract 318636: Survival in patients with refractory celiac disease and enteropathy associated T cell lymphoma.

Celiac disease is considered refractory when symptoms persist or recur despite adherence to a strict gluten free diet. Refractory sprue is divided into two types – type I and type II. Type I has a normal intraepithelial T lymphocyte population while the type II has an aberrant, intraepithelial T cell population. Type I seem to respond well to treatment like steroids, azathioprine, or immunosuppression. The type II not only don't respond to the gluten free diet, but they also don't respond to immunosuppressants and are in general more likely to transition to intestinal lymphoma. This study was aimed at providing further insight into refractory celiac disease and the evolution of intestinal lymphoma, and seeing what the long-term survival is of these patients. They studied a large group of patients with complicated celiac disease; 43 with refractory celiac type I and 50 with type II. In the type II group, 26 developed lymphoma after being refractory to gluten and 13 patients developed lymphoma independent from complicated celiac disease. The five year survival of type I was 96% while the five year survival in type II was 58% (p=0.001). In the population that went on to develop intestinal lymphoma, the five-year survival was only 8%. The bottom line is if you end up with type II refractory sprue and develop intestinal lymphoma, this is bad news. The two-year survival of the de novo intestinal lymphoma, not associated with celiac disease is 20% versus 15% in those secondary to celiac disease. Two-year survival of intestinal lymphoma is the same irrespective of whether there was associated disease or not. Overall, 28 from the 50 patients (56%) with type II refractory celiac disease died; twenty-three due to lymphoma, four from emaciation due to celiac disease and one from neuro celiac disease. So, if you are a refractory type I, you will not evolve into type II. If you are a refractory type II, you may evolve into intestinal lymphoma. Your prognosis is much, much worse.

Fortunately, refractory sprue is extremely rare. The majority of people that don't appear to respond to a gluten free diet actually are unknowingly sensitive even to traces of gluten. Before diagnosing refractory sprue, we have to be extremely careful; we do not have the clear, full understanding of the breadth of the possible permeation of gluten free products that can be cross-contaminated. When we have an individual that did not respond to a gluten free diet, particularly the ones that are still antibody positive (which means there is a process ongoing secondary to the exposure of gluten), I personally put them on what I call an elemental diet before I start treatment for refractory sprue with immunosuppressants. This is a diet in which you are not allowed to have gluten free products that are on the market, you cannot eat processed food, only food you prepare yourself in which there is no way there is cross-contamination of your food. We're talking about fresh meats, fresh fish, fresh fruits, fresh vegetables and oil. I have the patient stay on this diet for three to four months and in doing so, the vast majority of the time these people become antibody negative and the symptoms will go away. That proves that there was something that was sneaking into the diet that we could not find. From there, we start to build one food at a time. Of course, if you are dealing with refractory sprue, this will do nothing for your patients. They will continue to have symptoms and you do another biopsy and the problem is there. When you do the biopsy and you suspect refractory sprue, there is specific staining to look for the aberrant T-lymphocytes. They have very specific

surface markers that qualify them as aberrant. They express some CD markers in their surface that are not typically seen there. Going on a gluten free diet will become irrelevant to these people.

For type I, again, the management is with immunosuppressants. It's like dealing with IBD. You start with steroids to keep it under control and at the same time, you start with an immunosuppressant like azathioprine and then you taper down steroids and leave just the immunosuppressant there. In type II, unfortunately, everything has been tried – infliximab, monoclonal antibodies, etc. and failed. There is not much that we can do for these people. The chance that we will come across a patient with refractory sprue type II, fortunately, is not that high.

If you are dealing with a suspected diagnosis of refractory sprue, but the biopsy is not totally convincing, or there is not much damage, and of course the person does not respond to a gluten free diet, keep your mind open to alternative diagnoses. This may not be a person with celiac disease; it may be something else. Procedures like a double balloon endoscopy or videocapsule endoscopy would be appropriate. The key here is that we don't have markers to distinguish between one and the other, with one exception, which is addressed in the next abstract.

Abstract 318580: *The MYO9B gene is a strong risk factor for the development of refractory celiac disease.*

The same group found a strong association between the MYO9B and the risk to develop refractory sprue. This is the gene that seems to be associated with celiac disease; not the gene by itself but mutations in this gene. I don't want to go into too much detail, but there are mutations that now are screened by this technique that you sequence the entire genome or the gene including part of the gene that encodes and the part of the gene in between the encoding parts, the so called introns. They are not translated DNA, they are in between the parts that translate. So in other words, with many of the human genes, in this case myosin-9 beta, you may have a situation in which the gene is organized with the parts that actually encode the gene (exons) and those that are not translated (introns). But mutations (called SNPs) can be in these introns and as a matter of fact, you can find myosin-9 beta SNPs in those untranslated regions, so they are used as "markers" to distinguish a gene with this mutation and a gene without this mutation. This myosin-9 beta seems to have specific SNPs associated to celiac disease.

These investigators looked at the frequency of the SNPs among normal people, patients affected by classical celiac disease, and celiac patients with refractory celiac disease type I and type II. They did this analysis on 62 refractory sprue type II and looked at comorbidity with intestinal lymphoma, and 421 celiac disease classical patients, and 1624 controls. They genotype all these people, and again the number is not trivial given the rarity of the condition. They found that there were three SNPs of one in particular of this myosin-9 beta that was significantly different between refractory sprue type II with intestinal lymphoma compared to control ($p = 0.0002$). They also found the chance to develop type II with intestinal lymphoma to be higher in the people homozygous for DQ2.

This is the first evidence ever suggesting that we may have a genetic screening tool to identify people that may be at risk not only to develop celiac disease but to develop type II refractory sprue that can lead to intestinal lymphoma. This information right now is not clinically useful because as we have seen before, we do not have a solution for type II, but if we find a way to treat this, having this information will be valuable. We may have genetic chips that will tell us a series of risks and this is one example of very specific genetic analysis that seems complicated on paper, but it is relatively easy and fast so you can screen hundreds of people in a very short period of time.

The next abstract is very controversial. I had to select this one because we have always said that our gold standard to make the diagnosis of celiac disease is not the serology. We still need to do a biopsy regardless of whether we are dealing with an adult or a young patient. You must do an endoscopy with a biopsy to finalize the diagnosis.

Abstract 321532: *Small intestinal recovery is often incomplete in serum-negative celiacs during gluten free-diet.*

This is from a group in Italy. They are telling us that there is a possibility that our gold standard is not gold after all. There have been reports in the literature, and I am pretty sure if you are a pediatric or adult gastroenterologist you know, that the time of recovery of intestinal insult following a gluten free diet can be extremely variable. Some people recover in six months, some in two years. In the vast majority there is Marsh 1 damage, i.e. normal mucosa but increasing epithelial lymphocytes, even after years of gluten free diet. This is almost the norm. This group goes a little further and takes a look at the follow up biopsies on a large cohort and that is the strength of this abstract.

They looked at 484 celiac patients that were re-biopsied after their initial diagnosis. The second biopsy was done on average 32 + 2 months after the original biopsy and following a gluten free diet. The Marsh classification for the damage on diagnosis was 2% for Marsh 1, 4% for Marsh 2 and 94% for Marsh 3. In their experience, the vast majority of people at diagnosis have Marsh 3 damage. At the time they repeated biopsies, the patients were transglutaminase and endomysial antibody negative and the symptoms went away. Supposedly, these people have been taken care of. They have followed the gluten free diet correctly, the auto antibodies (i.e., TTG) are gone, and the symptoms have resolved. However, only 51 of these 456 patients in remission (a little bit more than 10%) had normal histology following implementation of a gluten free diet and that's scary. We're talking about almost three years of follow up; 11% were normal, 14% had Marsh 1 lesion, 53% had Marsh 2, and the remaining had Marsh 3, so in other words, the damage did not go away at all. If you go to 60 months, which is more than five years, still there will be issues here. In 80 patients on a gluten free diet for 25-60 months, they had people that still had significant damage, after such a long follow up. The question is, "What do we make of this and how are we going to handle this?"

There are several issues that this abstract raises. What is the value of antibodies for follow up? If I have a patient who has biopsy-proved celiac disease and they come to my practice with symptoms, I may find myself in a situation in which I put them on a gluten free diet, the symptoms resolve, the antibodies go away, and at a follow up endoscopy there is still Marsh 3 damage. What am I going to do with this patient? Are these people more at risk to develop intestinal lymphoma, type I diabetes, osteoporosis, or any other comorbidity that you can imagine associated with celiac disease because the damage is still there. There is no clear-cut way to treat these patients. In your clinical practice, if you have a patient that comes to you and has anemia for instance, you make the diagnosis of celiac disease based on serology and a Marsh 3 lesion, put them on a gluten free diet, the anemia is fixed, the antibodies go away, you decide to repeat an endoscopy and the biopsy is still positive, what's next? Are you going to scope this person routinely over time or will you just leave him/her alone? At this point we would not change therapy but clearly more work is needed.

Abstract 322682: *High rate of misinterpretation of histological diagnosis of celiac disease in the clinical practice.*

A retrospective analysis of 186 consecutive specimens referred for second opinion was performed. This abstract tells us that there is a tremendous misinterpretation of biopsies. Biopsy agreement by expert was 65%. Fifty-four (29%) were evaluated differently. Interobserver agreement was 0.38 (by Kappa). Six percent were not readable due to poor orientation of the specimen. There was an overestimation of celiac disease in the cohort they studied. They made the diagnosis of celiac disease much more frequently than they should. The take home message is that if you have the time and if you have the capability, review the biopsies yourself. Otherwise, you place your patients on a gluten free diet for the rest of their lives and they may not need it. I selected this abstract because I believe it is of benefit to take a look at the biopsies and request a second opinion if you are unsure. Combined with the previous abstract, it should be concluded that histology is not the gold standard diagnostic tool for celiac disease after all.

Abstracts Discussed

CONTROL ID: 321148: Is celiac disease different in the elderly compared to the young? I. Egbuna, P. Brar, P.H. Green, Celiac disease center, Columbia university college of physicians and surgeons, New York, NY

Background; Celiac disease over the years has shown a change in demographics from a disease of childhood to a disease of all ages. Few studies have been conducted looking specifically at presentation and disease characteristics in the elderly compared to a younger control population. Aims; to study the clinical presentations, pathological characteristics and associations of patients presenting with biopsy confirmed celiac disease in the elderly. Methods; A review of patients (n =1008) from a prospectively generated database was performed on all patients presenting with biopsy confirmed celiac disease at ages ≥ 65 years. Mode of presentation, duration of symptoms, clinical findings, small intestinal pathology, associated medical illnesses including autoimmune diseases were evaluated and compared to a subpopulation of patients diagnosed at ages 18 – 30 years. Both populations were evaluated for significant differences to try to define elderly presentation. (Mann-Whitney rank sum test and Pearson correlation were used) Results; Elderly patients (n = 125) were compared to young adults (n = 149). There was a female predominance in both age groups (male: female = 1:1.3 vs. 1: 3.9 for elderly vs. younger). Female predominance was more marked in the younger age group (79% vs. 57% females $p < 0.001$) with a trend toward more males in the older age group. There was no difference in the mode of presentation between the groups (diarrhea 50 % vs. 50 % silent/atypical) in the elderly vs. (diarrhea 48 % vs. 52 % silent /atypical) in the younger group. There was no difference in duration of symptoms prior to presentation (6.1 yrs \pm 12.6 vs. 5.8 yrs \pm 12.0; $p = 0.119$ in the elderly vs. younger groups respectively), nor degree of villous atrophy. A greater percentage of females tended to present with diarrhea in both groups (63% vs. 85%; ≥ 65 yrs vs. 18-30 yrs) with no statistically significant difference. The prevalence of males presenting with diarrhea was higher in the elderly group vs. the younger group (37% vs. 15%; $p = 0.006$). There was no difference between the two groups in overall autoimmune disease ($p = 0.133$), however there was a higher prevalence of thyroid disease and neuropathy in the older population compared to the younger population (14% vs. 7%, $p = 0.037$) and (11% vs. 4%, $p = 0.023$) respectively. Conclusions; The characteristics of celiac disease in the elderly are similar to those in young adults apart from a greater male presence in the elderly and a greater prevalence of thyroid disease and neuropathy. It is unclear why patients present at any given age. Studies need to be conducted to identify factors responsible for triggering presentation.

CONTROL ID: 318695: PREVALENCE OF HUMAN ANTI-TRANSGLUTAMINASE ANTIBODIES (h-TGA) IN PATIENTS WITH UNEXPLAINED INFERTILITY AND INFERTILITY WITH A KNOWN CAUSE. E. Rondonotti, V. Saladino, C. Folli, S. Saibeni, University of Milan, IRCCS Fondazione Policlinico, Mangiagalli, Regina Elena, Milan, ITALY; F. Cavallaro, M. Vecchi, University of Milan, IRCCS Policlinico S. Donato, Milan, ITALY; G. Ragni, R. Borroni, A.E. Nicolosi, Infertility Unit, University of Milan, IRCCS Fondazione Policlinico, Mangiagalli, Regina Elena, Milan, ITALY

BACKGROUND: Several infertility problems have been previously reported in patients (particularly women) with celiac disease (CD). Anti human transglutaminase antibodies (h-TGA) assay is the most sensitive test for CD diagnosis. AIM: To evaluate the prevalence of h-TGA in patients with unexplained infertility (UI) and patients with infertility with a known cause (IWKC). PATIENTS: We enrolled 86 UI patients (43 men, 43 women) and 376 (240 men, 136 women) IWKC patients. METHODS: We screened all the enrolled patients with h-TGA; all h-TGA positive patients were planned for duodenal biopsy. RESULTS: 6 patients were h-TGA positive (6/462; 1.3%). So far, 3 h-TGA positive patients have undergone duodenal biopsy that showed villous atrophy in all. 2 out of 86 UI patients (2.3%) and 4 out of 376 IWKC patients (1.0%) were h-TGA positive ($p = 0.31$). Two out of 46 (4.6 %) men and none of 43 women with UI were h-TGA positive ($p = 0.49$). Among 240 men with IWKC, 1 (0.4%) was h-TGA positive while 3 out of 136 (2.2%) women with IWKC were h-TGA positive ($p = 0.13$). CONCLUSIONS: In this large series of infertile patients the prevalence of h-TGA is 1.3%. The prevalence of h-TGA is particularly high (4.6 %) in men with UI.

CONTROL ID: 318636 : Survival in patients with Refractory Celiac Disease and Enteropathy associated T cell Lymphoma. W. Verbeek, A. Al-Toma, M. Hadithi, C.J. Mulder, Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, NETHERLANDS; M. von Blomberg, Pathology, VU University Medical Center, Amsterdam, NETHERLANDS

Background: Celiac disease may be regarded as refractory disease (RCD) when symptoms persist or recur despite strict adherence to a gluten free diet. RCD may be subdivided into types I and II with a phenotypically normal and aberrant intraepithelial T-cell population, respectively. RCD I seems to respond well to azathioprine/prednisone therapy. RCD II is usually resistant to any known therapy and transition into Enteropathy-Associated T-cell Lymphoma (EATL) is common. Aim: The aim of this study is to provide further insight into RCD and the development of EATL, by reporting on long-term survival, risk of transition of RCD into EATL in one of the largest cohorts of patients with complicated celiac disease in a single center. Design and Methods: We have retrospectively compared four groups of patients with complicated celiac disease: 43 RCD-I, 50 RCD II (total), of whom 26 RCD II who developed EATL after a period of refractoriness to a gluten free diet (secondary

EATL) and 13 EATL patients without preceding history of complicated celiac disease (de novo EATL). Every effort was made to ensure correct classification and accurate patient allocation. Results: No celiac disease related mortality is recognized in the RCD I group. The overall five-year survival in RCD I is 96%, in RCD II (total) is 58% (P=0.001) and in RCD II after developing EATL is only 8%. The 2 year survival in the de novo EATL is 20% versus 15% in secondary EATL (P=0.63). Twenty eight (56%) from 50 patients with RCD-II died, 23 (46%) due to EATL and 4 due to progressive refractory state with emaciation and one from neuro celiac disease. Conclusion: Remarkably, no patient with RCD I developed RCD II or EATL within mean follow up of five years (range 2-15 years). Fifty two percent of the RCD II patients developed EATL within 4-6 years after the diagnosis of RCD II. More aggressive therapy seems necessary in RCD II and EATL.

CONTROL ID: 318580 : The MYO9B gene is a strong risk factor for the development of refractory celiac disease. W. Verbeek, C.J. Mulder, Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, NETHERLANDS; V.M. Wolters, Pediatric Gastroenterology, UMC , Utrecht, NETHERLANDS; A. Zhernakova, C. Onland-Moret, A.J. Monsuur, C. Wijmenga, Complex Genetics Section, Department of Medical Genetics, UMC , Utrecht, NETHERLANDS; M.W. Schreurs, Pathology, VU University Medical Center, Amsterdam, NETHERLANDS; W. Verduijn, Immunohaematology and Bloodtransfusion, Leiden University Medical Center, Leiden, NETHERLANDS

Background & Aims: Celiac disease (CD) is associated with HLA-DQ2 and HLA-DQ8 and has been linked to genetic variants in the MYO9B gene on chromosome 19. HLA-DQ2 homozygosity is associated with complications of CD such as refractory celiac disease type II (RCD II) and enteropathy-associated T-cell lymphoma (EATL). We investigated whether MYO9B also predisposes to RCD II and EATL. Methods: Genotyping of MYO9B and molecular HLA-DQ2 typing was performed on 62 RCD II and EATL patients, 421 CD patients and 1624 controls. Results : Three SNPs in MYO9B showed a significantly different allele distribution in RCD II and EATL patients compared to controls (p=0.00002, 0.05 and 0.04, respectively). The rs7259292 T allele was significantly more frequent in RCD II and EATL patients compared to CD patients (p=0.0003, OR 3.61 (95% CI 1.78-7.31)). The frequency of the haplotype carrying the T allele of this SNP was significantly increased in RCD II and EATL patients (11%), compared to controls (2%) and CD patients (3%) (OR 6.76 (95% CI 3.40–13.46), p=2.27E-09 and OR 4.22 (95% CI 1.95–9.11) p=0.0001, respectively). Both MYO9B rs7259292 and HLA-DQ2 homozygosity increase the risk for RCD II and EATL to a similar extent when compared to CD patients (OR 4.3 (95% CI 1.9–9.8) and 5.4 (95% CI 3.0–9.6), respectively) without evidence for interaction between these two risk factors. Conclusion: This study shows that both MYO9B and HLA-DQ2 homozygosity might be involved in the prognosis of CD and the chances to develop RCD II and EATL.

CONTROL ID: 321532: Small intestinal recovery is often incomplete in serum-negative celiacs during gluten free-diet. A. Lanzini, F. Lanzarotto, A. Mora, S. Bertolazzi, F. Benini, C. Ricci, Medicine, University-Spedali Civili Brescia, Brescia, ITALY; V. Villanacci, Hystopathology, Spedali Civili Brescia, Brescia, ITALY

It has been suggested (Gastrointest Endosc 2003; 57: 187-91) that complete histopathologic recovery may be the exception and not the rule in celiac patients during gluten free diet (GFD), but the evidence is conflicting (Gastrointest Endosc 2004; 59: 158-9). Furthermore, incomplete recovery with persistence of intraepithelial lymphocytosis during GFD is potentially attributable to factors independent of celiac disease, i.e. Helicobacter pylori infection (Arch Pathol Lab Med 2006; 130: 1020-5). The aim of our study was to review the effect of GFD on duodenal histopathology in a large number of celiacs studied before and during GFD, and to assess the role of Helicobacter pylori infection. We carried out follow-up duodenal biopsy in 484 celiac patients 32 + 2 months (mean + SEM; median 18 months) after starting gluten-free-diet (GFD). Prior to GFD 2%, 4% and 94% of patients were classified as Marsh 1, 2 and 3 at duodenal histopathology, respectively. At the time of follow-up biopsies 456 patients were tissue –transglutaminase (t-TG) and/or endomysial antibodies (EMA) negative during GFD. Only 51 of these 456 seronegative patients had normal duodenal histopathology during GFD, and the proportion changed slightly according to the length of GFD. Histopathology was normal in 11%, and Marsh 1, 2 and 3 lesions persisted in 14%, 53% and 22% of 332 patients on GFD for 12-24 months. The corresponding values were 10%, 15%, 57% and 18% in 80 patients on GFD for 25 to 60 months, and 21%, 24%, 33%, 22% in 67 patients on GFD for longer than 60 months, respectively (p<0.004 by Chi-squared test for independence). TTG/EMA were negative at the time of follow-up biopsy in 75/92 CD with persistent Marsh 3 lesion during GFD. Gastric biopsies were obtained in addition to duodenal biopsies in 432 patients at follow-up. The proportion of Marsh 1 and 2 lesion was similar in patients with Helicobacter pylori infection (62%) as in those without infection (69%). We conclude that (i) Marsh 1 and 2 lesions persist in the majority of CD patients during GFD despite negative serology and clinical improvement; (ii) this persistence is independent of Helicobacter pylori infection; (iii) there is a tendency for prevalence of abnormal histopathology to decrease during prolonged dietary treatment; (iv) t-TG and EMA are poor predictors of complete histopathologic recovery of duodenal mucosa during GFD.

CONTROL ID: 322682: High rate of misinterpretation of histological diagnosis of celiac disease in the clinical practice. I. Pinto, E. Smeccol, R. Mazure, A. Cabanne, S. Niveloni, E. Mauriño, J.C. Bai, Medicine, Gastroenterology Hospital, Ciudad Autonoma de Buenos Aires, ARGENTINA

BACKGROUND/AIM: The histological analysis of small bowel mucosa is considered the gold standard for diagnosing celiac disease (CD). However, misinterpretation of specimens maybe source of potential pitfalls in clinical practice. Thus, poor sample quality, inadequate orientation and cutting could determine over- or under- interpretation of intestinal morphology. Our aim in the present study was to analyze the histological diagnostic performance in clinical practice reviewing a series of intestinal biopsies studied by general pathologists. **MATERIAL AND METHODS:** We performed a retrospective analysis of 186 consecutive specimens from patients referred for a second opinion to a tertiary center from September 2003 to October 2006. Original pathologic reports produced by many different clinical pathologists were retrieved. Characterization of CD by the expert reviewer was based on morphological grounds (Marsh's type II or greater enteropathy). According to original reports, 129 samples had been considered as compatible with CD and 57 as having normal histology. Agreement was also established according to the Cohen's kappa statistics for dichotomy variables. **RESULTS:** According to the expert review, 12 samples (6.4%) were not valuable at all because bad or poor quality of specimens. Both, original pathological reports and the review agreed diagnosis in 120 samples (64.5%). This included 77 specimens identified as CD and 43 having normal histology. Respect to original reports, 54 specimens (29.0%) had a divergent diagnosis by the expert pathologist (final diagnosis was CD in 11 and normal histology in 43). Using the kappa statistic, inter-observer agreement was 0.38. Based on the final diagnosis, misinterpretation was mainly produced by an over-diagnosis as CD of normal histological samples (40% vs. 25%; OR 0.48, 95% CI 0.24-0.97; $p < 0.05$). **CONCLUSIONS:** Our study detected major differences in the histopathological assessment of small intestinal biopsies between non-experienced and expert pathologists. Overall, misinterpretation by general pathologists was produced in 35.5% of specimens. These pitfalls in clinical practice may have profound negative implications for patients.