Challenges in the Diagnosis and Management of Celiac Disease

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Diagnoses of celiac disease continue to rise, and despite the increased awareness of the disease, most patients in the United States remain undiagnosed [Ludvigsson JF et al. *Am J Gastroenterol*. 2013]. Population studies suggest that about 1% of the general population has celiac disease [Rubio-Tapia A, Murray JA. *Gut*. 2010], yet the proportion of patients undiagnosed has been estimated to be between 83% and 95% [Rubio-Tapia A et al. *Am J Gastroenterol*. 2012; Catassi C et al. *Ann Med*. 2010]. Benjamin Lebwohl, MD, MS, Columbia University, New York, New York, USA, discussed the difficulties of diagnosing celiac disease.

For serologic testing, the tissue transglutaminase (tTG) immunoglobulin A (IgA) has the greatest sensitivity (about 86%) and specificity (about 99%) [Hopper AD et al. *Clin Gastroenterol Hepatol*. 2008] but may miss those patients with a low total IgA. Therefore, immunoglobulin G (IgG) serologies can be used, with deamidated gliadin peptide IgG having the best performance. The tTG IgG test has a lower specificity and can result in a false positive. Patients with an isolated elevated deamidated gliadin peptide IgA most likely do not have celiac disease [Suarez AL et al. DDW 2015 (abstr Sa1289)]. Dr Lebwohl discussed several strategies for serologic testing, including when it indicates a need for biopsy (Table 1).

False-negative biopsies are common and can happen due to the following: patchy disease, subtle histology that is missed by the pathologist, having a long-term gluten-free diet (GFDs) before undergoing the esophagogastroduodenoscopy (EGD), or an insufficiently biopsied duodenum during the EGD. Yet, false positives occur as well and are most commonly caused by overreliance on positive serology, poorly oriented specimens, overinterpretation of nonspecific findings, and presence of other conditions that cause villous atrophy. Other causes of villous atrophy include drugs such as olmesartan and mycophenolate, Crohn disease, giardia, tropical sprue, bacterial overgrowth, HIV, autoimmune enteropathy, and common variable immunodeficiency. In patients who have negative serology but a positive biopsy, gene testing for *DQ2* or *DQ8* can be performed, as 100% of patients with celiac disease will be positive vs 40% of the general population, stated Dr Lebwohl.

During EGD, it is important that the duodenum is biopsied, which is performed in < 50% of procedures [Lebwohl B et al. *Gastrointest Endosc*. 2012]. In addition, 4 to 6 specimens should be submitted, yet ≥ 4 specimens are submitted in only 35% of patients [Lebwohl B et al. *Gastrointest Endosc*. 2011]. However, the sensitivity of biopsy for celiac disease diagnosis increases with an increasing number of biopsy specimens. In addition, a 1-bite-per-pass technique may improve the orientation of the specimens [Latorre M et al. *Gastrointest Endosc*. 2015]. Dr Lebwohl advised against omitting a biopsy in children who have positive serology or gene testing because of potential difficulties later, such as recurrence of symptoms.

Patients who have been on a GFD for years pose a challenge for diagnosing celiac disease. In these cases, human leukocyte antigen *DQ2* or *DQ8* testing has a negative predictive value of almost 100%, noted Dr Lebwohl. Recent data suggest that a 2-week gluten challenge consisting of just 2 slices of bread per day can result in substantial changes in villous structure at the end of the challenge; however, tTG IgA levels do not rise until about day 28 [Leffler DA et al. *Gut*. 2013].

Once celiac disease is diagnosed and a GFD initiated, up to 19% of patients will continue to experience gastrointestinal (GI) or non-GI symptoms [Leffler DA et al. *Clin Gastroenterol Hepatol*. 2007]. Joseph A. Murray, MD, Mayo Clinic, Rochester, Minnesota, USA, discussed the management of patients who have persistent symptoms or who experience only a partial recovery. Some patients, even those who initially respond to a GFD, may have been misdiagnosed as having celiac disease but may have another condition.

In addition, barriers to remaining on a GFD include cross-contamination with hidden gluten sources; social, professional, and psychological well-being; cost; the burden of reading

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Table 1. Strategies for Diagnosing Celiac Disease

Serologic Test: Result	Next Step
tTG IgA and total IgA	
Positive tTG	Biopsy
Negative tTG, normal IgA	Stop
Negative tTG, low IgA	Order DGP IgG
tTG IgA and DGP IgG	
Positive tTG, positive DGP	Biopsy
Negative, tTG, negative DGP	Stop

DGP, deamidated gliadin peptide; IgA, immunoglobulin A; IgG, immunoglobulin G; tTG, tissue transglutaminase.

Table 2. VU University Medical Center Experience in Treatment of Pre-EATL

Treatment	n	Median Follow-up, mo	EATL Rate, %
2-CDA monotherapy[a]			
IIIa-c	12	64	60
0-I	14	58	8*
2-CDA-BMT combination therapy	15	78	7

2-CDA, 2 cycles of cladribine; BMT, budesonide; EATL, enteropathy-associated T-cell lymphoma.

[a]By Marsh classification.

*$P = .01$ vs 2-CDA monotherapy group and $P = .80$ vs 2-CDA-BMT combination therapy.

labels; access to gluten-free foods; and nutritional content [Leffler DA et al. *Clin Gastroenterol Hepatol*. 2009]. Indeed, in one study, about 70% of patients with celiac disease reported gluten exposure while on a GFD, with about 28% not having intentional or known inadvertent exposures [Hall NJ et al. *Appetite*. 2013].

Persistent or recurrent symptoms may be caused from other conditions, such as small intestinal bacterial overgrowth (SIBO). In one 2003 study, 67% of patients with celiac disease and persistent symptoms had SIBO. In a study in 2004, GI symptoms improved with SIBO treatment.

Noncompliance with a GFD may be associated with increased mortality, osteoporosis, cancer (including lymphoma), and adverse psychological effects. Conversely, persistent villous atrophy while on a GFD does not appear to be associated with increased mortality [Lebwohl B et al. *Ailment Pharmacol Ther*. 2013]. However, a GFD can reverse villous atrophy. Complete mucosal recovery may be achieved by up to 95% of children within 2 years, as shown in a 2002 study; however, complete recovery appears to be less achievable and takes longer in adults, as shown by Rostom and colleagues in 2006.

The management of refractory celiac disease is important because 60% to 80% of these patients will develop enteropathy-associated T-cell lymphoma (EATL) [Wierdsma NJ et al. *Clin Nutr*. 2015], stated Chris J. Mulder, MD, VU University Medical Center, Amsterdam, The Netherlands. In type I refractory celiac disease, the risk of developing EATL is low; more patients with type II refractory celiac disease develop EATL [Nijeboer P et al. *Gastroenterol Res Pract*. 2013]. Positron emission tomography (PET) is essential for diagnosis of EATL, as refractory celiac disease without EATL will be PET negative. T-cell flow with CD8+ T cells >20% or immunohistochemistry revealing an abnormal CD3:CD8 intestinal lymphocyte ratio is more likely to develop complications such as EATL.

The treatment of patients with pre-EATL includes cladribine. If response is seen after 3 to 6 months, then patients undergo follow-up. Nonresponders who are generally aged <70 and successfully undergo leukapheresis receive autologous stem cell transplant. Budesonide (not slow release) was recently added to cladribine at the VU University Medical Center, said Prof Mulder. Of the patients treated, EATL developed at different rates depending on treatment response (Table 2).

However, Prof Mulder noted that patients with pre-EATL have heterogeneous disease, with a proportion with interleukin 15rα or 15rβ expression [Schmitz L et al. *Gut*. 2015. In press]. Therefore, the treatment strategies of these expression types may be different in the future. For example, tofacitinib is undergoing evaluation for interleukin 15rβ–expressing pre-EATL.

For the treatment of patients with EATL, Prof Mulder discussed a planned phase 2 trial that will evaluate brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone in European patients [Sibon D et al. ASH 2013 (poster 4252)]. Nonresponders will receive methotrexate, and if still no response is observed, they will receive carmustine plus etoposide, cytarabine, and melphalan, followed by autologous stem cell transplantation. Currently, therapy for EATL includes cyclophosphamide, doxorubicin, vincristine, and prednisone plus methotrexate, which yields a very poor 5-year survival rate of approximately <10% [Nijeboer P et al. *Am J Hematol*. 2015]. One alternative is cyclophosphamide, doxorubicin, and prednisone plus brentuximab, methotrexate, and bendamustine.

In conclusion, celiac disease can be challenging to diagnose and manage. A GFD is important to maintain, as noncompliance is associated with increased morbidity and possibly mortality. Refractory celiac disease is associated with EATL, which has a high mortality rate despite treatment.