Diagnostic Delay, Small Bowel Villous Atrophy, and Gluten Challenge in Dermatitis Herpetiformis

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Eriika Mansikka, MD, conducted her PhD studies at Department of Dermatology and Venereology, Tampere University Hospital, Finland during the period 2015-2019. Her dissertation was held on October 25, 2019 at Tampere University. *Supervisors*: Professor Timo Reunala, Docent Teea Salmi, and Docent Kaisa Hervonen. *Opponent*: Professor Kaisa Tasanen-Määttä from the University of Oulu, Finland. Link to complete thesis: https://trepo.tuni.fi/bitstream/handle/10024/116843/978-952-03-1217-6.pdf?sequence=2&isAllowed=y

Dermatitis herpetiformis (DH) is an extraintestinal manifestation of coeliac disease presenting with an intensely itchy and blistering rash mainly on the elbows, knees, and buttocks. Diagnosis is based on the demonstration of granular IgA deposits in the papillary dermis by examination with direct immunofluorescence (IF). The disease is caused by gluten, a protein found in wheat, rye, and barley, which initiates an autoimmune response in genetically predisposed individuals. This leads to small bowel mucosal damage typical of coeliac disease and, in some individuals, to a blistering rash typical of DH. At present, 13% of adults with coeliac disease have DH in Finland. The incidence of DH is decreasing, whereas the reverse is true for coeliac disease. The mainstay of treatment for DH and coeliac disease is a life-long gluten-free diet (GFD), which in DH also heals the rash.

In the research presented in the present dissertation, a cohort of patients with DH diagnosed between 1970 and 2014 at Tampere University Hospital, Finland were investigated. The first aim was to evaluate diagnostic delay in DH. The second aim was to study whether small bowel histological findings have changed over the 45-year period and to determine how mucosal damage correlates to serum transglutaminase 2 (TG2) antibody levels. The third aim was to examine if the presence or absence of small bowel villous atrophy at diagnosis affects the long-term prognosis of DH patients on a GFD. The fourth aim was to examine, by gluten challenge, whether DH patients on a long-term GFD treatment could have developed gluten tolerance, as suggested by a few earlier studies.

The dissertation consists of 4 separate studies. In Study I, the duration of the rash before diagnosis was examined from hospital records in 446 DH patients. The diagnosis was considered delayed when the duration of the rash before diagnosis was two years or longer. Factors associated with the delayed diagnosis were analysed in more detail using follow-up questionnaires obtained from 217 patients. Over the study period, the median duration of the rash before diagnosis decreased

Fig. 1. From left to right: Professor Timo Reunala, Professor Kaisa Tasanen-Määttä, Docent Teea Salmi, MD Eriika Mansikka and Associate Professor Kaisa Hervonen.

and the number of patients with delayed diagnosis decreased. Female gender and the presence of villous atrophy correlated with the delayed diagnosis, whereas age at diagnosis and the activity of the rash did not. According to the follow-up questionnaire, bone fractures or malignancies were shown not to occur more often in those patients with a delayed diagnosis compared to those with a non-delayed diagnosis.

In Study II, the severity of small bowel villous atrophy was examined in 393 DH patients over the 45-year study period. The prevalence of severe (subtotal/total) villous atrophy (SVA) was shown to decrease over time. At the same time, an increase was seen in both partial villous atrophy (PVA) and normal villous architecture. Patients with villous atrophy had higher TG2 antibody levels than those with normal villous architecture. However, several patients with villous atrophy had normal TG2 antibody levels, indicating that a negative test result does not always exclude villous damage in DH.

In Study III, long-term prognoses were compared between DH patients with and without small bowel villous atrophy at diagnosis (n=352) and 128 coeliac disease controls. Initial data was gathered from the patient records and follow-up data was collected via questionnaires from 181 DH patients on a GFD. At the DH diagnosis, 98 (28%) patients had normal villous architecture and 254 (72%) had villous atrophy. Clinical recovery did not differ significantly between the DH groups, nor did the presence of long-term illnesses, coeliac disease-related complications or quality of life (QoL). By contrast, the coeliac disease controls had osteopenia/osteoporosis, thyroid diseases and malignancies more often compared to the DH patients.

In Study IV, 19 asymptomatic DH patients who had adhered to a GFD for a mean of 23 years were challenged with gluten for up to 12 months. Before the challenge skin biopsies showed negative IgA and transglutaminase 3 (TG3) deposits in 84% of the patients and normal villous mucosa in all of them. The gluten challenge caused a relapse of the rash and/or villous atrophy in 18 (95%) DH patients; 15 (79%) patients showed a rash within a mean of 5.6 months and 3 (16%) had only small bowel villous atrophy.

The results of the present dissertation show that diagnostic delay in DH has decreased over time. Further, the prevalence of SVA decreased during the 45-year study period and high serum TG2 antibody levels reveals rather well whether the patients have villous atrophy. However, the presence of villous atrophy at the time of diagnosis was shown not to effect GFD treatment response or long-term morbidity and QoL and hence has no effect on the prognosis of DH. Importantly, the gluten challenge showed that a life-long GFD treatment remains justified in all DH patients.

List of original publications

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

I. Mansikka E, Salmi T, Kaukinen K, Collin P, Huhtala H, Reunala T, Hervonen K. Diagnostic delay in dermatitis herpetiformis in a high-prevalence area. Acta Derm Venereol 2018; 98: 195–199.
II. Mansikka E, Hervonen K, Salmi TT, Kautiainen H, Kaukinen K, Collin P, Reunala T. The decreasing prevalence of severe villous atrophy in dermatitis herpetiformis: a 45-year experience in 393 patients. J Clin Gastroenterol 2017; 51: 235–239.
III. Mansikka E, Hervonen K, Kaukinen K, Collin P, Huhtala H, Reunala T, Salmi T. Prognosis of dermatitis herpetiformis patients with and without villous atrophy at diagnosis. Nutrients 2018; 10: 641.
IV. Mansikka E, Hervonen K, Kaukinen K, Ilus T, Oksanen P, Lindfors K, et al. Gluten challenge induces skin and small bowel relapse in long-term gluten-free diet treated dermatitis herpetiformis. J Invest Dermatol 2019, Apr 15 Epub ahead of print.