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Severity of villous atrophy at diagnosis in childhood does not predict long-term outcomes in celiac disease

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Abbreviations: BMI, body mass index; EmA, endomysium antibody; ESPGHAN, European Society for Pediatric Gastroenterology Hepatology and Nutrition; GSRS, Gastrointestinal Symptom Rating Scale; PGWB, Psychological General Well-Being Questionnaire; PVA, partial villous atrophy; SD, standard deviation; SVA, subtotal villous atrophy; TG2ab, transglutaminase 2 antibody; TVA, total villous atrophy.

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Abstract

Objectives: Current pediatric guidelines allow non-invasive diagnosis of celiac disease in selected children. We investigated in a large cohort study whether the severity of villous atrophy at diagnosis is associated with clinical characteristics or long-term health outcomes, thus having a prognostic significance.

Methods: Comprehensive medical data on 906 children with celiac disease were analyzed. Long-term health outcomes of 503 adult patients diagnosed in childhood were moreover assessed with a specific study questionnaire and validated GSRS and PGWB questionnaires. Patients were classified into three groups according to severity of villous atrophy at diagnosis and all variables were compared.

Results: Altogether 34% of the patients had partial, 40% subtotal, and 26% total villous atrophy. Children with milder lesions were diagnosed more recently (median year 2007 vs. 2006 vs. 2001 respectively, $p<0.001$), more often by screening (30% vs. 25% vs. 17%, $p<0.001$) and they suffered less often from anemia (16% vs. 21% vs. 32%, $p<0.001$) and growth disturbances (22% vs. 36% vs. 54%, $p<0.001$) and had lower transglutaminase-2 antibody levels (median 64 U/l vs. 120 U/l vs. 120 U/l, $p<0.001$). There was no difference in other disease features.

Altogether 212 adults diagnosed in childhood completed the questionnaires. Severity of villous atrophy at childhood diagnosis did not predict presence of complications or comorbidities, persistent symptoms, and self-perceived health, quality of life or adherence to a gluten-free diet in adulthood.

Conclusions: Presence of advanced villous atrophy at diagnosis is associated with more severe clinical characteristics but not with poorer long-term health and treatment outcomes.

Key Words: Adulthood; Biopsy; Celiac Disease; Childhood; Follow-up.

What is known

- According to the current ESPGHAN guidelines, diagnosis of celiac disease can be established in selected children without duodenal biopsy.
- In adults, more severe mucosal damage in duodenum at diagnosis has been reported to predict delayed mucosal healing and poorer treatment outcomes.

What is new

- Children with more severe villous atrophy at the time of celiac disease diagnosis had a more severe disease as regards anemia, growth disturbances, and serology.
- Severity of villous atrophy at diagnosis was not associated with long-term health and treatment outcomes, including self-perceived health, health-related quality of life and presence of comorbidities, complications, and persistent symptoms.

Introduction

Celiac disease is a common immune-mediated condition in which effective diagnostics and optimal treatment outcomes are of major public health significance.[1] Diagnosis has long been based on the demonstration of characteristic lesions of intestinal mucosa. However, a tendency towards a less invasive diagnostic approach, together with the development of serological tests, has led to the introduction of serology-based guidelines by the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN).[2] The recent update of these criteria allows omission of biopsy in children with transglutaminase 2 antibody (TG2ab) values >10x the upper limit of normal and positive endomysium antibodies (EmA) regardless of the clinical presentation.[3]

Recent prospective studies support the reliability of the ESPGHAN guidelines,[4,5] but there are also some contradictory results and criticism.[6] Furthermore, arguments in favor of biopsy may be other than purely diagnostic. One of these is the easier assessment of histological recovery in dietary treatment, although in children a repeat biopsy is rarely performed.[7] Moreover, in adults severe small bowel damage and clinical presentation at diagnosis have been reported to predispose respectively to slower mucosal recovery[8] and suboptimal dietary response.[9] These issues could be particularly relevant in growing children. It has even been suggested that the severity of the mucosal damage could be associated with long-term prognosis.[10] If baseline biopsy had any real prognostic value, it could be used to design a more personalized follow-up, but evidence is lacking. In fact, even the association between the severity of histological changes and other diagnostic and clinical characteristics of pediatric celiac disease has scarcely been studied.[11,12]

Finland has a long history of celiac disease research, as well as unified diagnostic criteria and high prevalence. This enabled us to study a large and well-defined cohort of pediatric celiac disease patients with follow-up data in adulthood.[13,14] We utilized this data and specific questionnaires to investigate whether the severity of villous atrophy at diagnosis is associated with clinical characteristics or long-term health outcomes in celiac disease.

Materials and methods

Patients and study design

The study was conducted in Tampere University and Tampere University Hospital. The hospital is a tertiary center for a population of approximately 900,000 people, including 145,000 children, and is the main referral site for children with suspected celiac disease.

The basis of the study cohort was a comprehensive dataset of 1,096 patients with childhood celiac disease diagnosed between 1966 and 2014. (Figure 1) The dataset was formed by collecting patient data systemically from medical records and, if needed, supplementing it. Altogether 118 patients were excluded due to uncertain diagnosis or insufficient clinical data, and a further 72 due to lack of precise histological data. Thereafter, clinical characteristics of 906 pediatric patients were compared according to the severity of villous atrophy. (Figure 1)

Association between baseline mucosal damage and long-term health and treatment outcomes was evaluated with the help of specific questionnaires. These were sent to 503 adult patients (age ≥18y in September 2016) from the initial dataset of subjects diagnosed in childhood with available contact information. To improve the response rate, the questionnaires were re-sent to all non-responders after two months. (Figure 1) To estimate the possible selection bias, the medical record data available were compared between responders and non-responders.

Disease characteristics at diagnosis in childhood

Medical data at the time of celiac disease diagnosis were retrieved from patient records. These included the results of histopathological assessment of the small bowel morphology confirming the diagnosis, clinical presentation including presence and nature of symptoms, presence of complications, and values of blood hemoglobin and celiac disease specific antibodies.

At least four representative duodenal biopsy samples were obtained with Watson aspiration capsule before 1986 and thereafter through esophagogastroduodenoscopy. From 2013 onwards samples from duodenal bulb have also been taken. The biopsies were processed and mucosal abnormalities evaluated from sections cut after careful orientation of the specimens.[15] The severity of diagnostic villous atrophy was classified on the basis of the original pathology report as partial (PVA), subtotal (SVA) or total (TVA) villous atrophy as this classification has systematically been used in our clinical practice during the whole study period from the 1960s.[16] All study variables were compared between patients assigned to these three histological groups.

The main clinical presentation of celiac disease was further divided into 1) gastrointestinal, such as diarrhea, abdominal pain, constipation, and vomiting, 2) extra-intestinal, e.g. arthralgia, growth disturbances, anemia, and dermatitis herpetiformis, and 3) screen-detected, including those screened for celiac disease due to belonging to a high-risk group such as patients with type 1 diabetes or family history of celiac disease.

Poor growth was defined as impaired growth velocity in the longitudinal evaluation of growth charts and/or impaired height or weight development when compared to the gender and age dependent reference values or parental height.[17,18] Height was expressed with standard deviation (SD) scores, which compare the height of a child to the average height of Finnish children of the same age.[17] Body mass index (BMI) was calculated as kg/m^2. Percentile values for age or z-scores were not used, but possible differences in age or gender between the groups were adjusted in statistical analyses. Anemia was defined as blood hemoglobin value (g/L) lower than the age and gender-specific reference value.

The values of serum EmA and TG2ab at diagnosis were collected systematically from the year 2000 onward. During this time in our settings, EmA was determined by indirect immunofluorescence.[19] A serum dilution of 1: ≥5 was considered positive and positive samples were further diluted 1:50, 1:100, 1:200, 1:500, 1:2000 and 1:4000. TG2abs were measured either by ELISA

(Phadia AB, Uppsala, Sweden) or by an automated enzyme fluoroimmunoassay (Phadia). Values 7 U/L or higher for TG2abs were considered positive. Serum antigliadin and antireticulin antibodies were formerly widely used but, due to their unsystematic use and inferior diagnostic accuracy, they were not collected here.[20]

Disease characteristics in adulthood

Celiac disease patients who were adults at the time of the study were invited to complete three questionnaires. The first was a specific study questionnaire evaluating the presence of complications and comorbidities related to celiac disease, possible ongoing symptoms, general health, health-related concerns, adherence to a gluten-free diet, and experience of the diet to cause restrictions in daily life. Socioeconomic and lifestyle factors such as employment status and level of education, presence of children, membership of a celiac society, smoking status, use of prescription medication, and regularity of physical exercise, were also studied.

Dietary adherence was categorized as 1) strict diet (lapses extremely rarely or never) and 2) lapses/no diet. Self-perceived health was divided into 1) excellent or good, and 2) moderate or poor, and health-related concerns to 1) nonexistent or mild and 2) moderate or severe.[14,21]

Presence and severity of ongoing gastrointestinal symptoms were assessed by the validated Gastrointestinal Symptom Rating Scale (GSRS), comprising 15 questions covering five sub-dimensions: diarrhea, indigestion, constipation, abdominal pain, and reflux. A seven-point Likert scale was used to rate the symptoms from none (1) to severe (7). Total GSRS score is the mean of all 15 items and each sub-dimension is calculated as a mean of related items.[22–24]

Self-perceived quality of life was evaluated with the validated Psychological General Well-Being questionnaire (PGWB). The survey contains 22 questions covering six sub-categories: anxiety, depression, well-being, self-control, general health, and vitality. A six-point Likert scale (1-

6) is applied to rate the answers, higher score indicating better well-being. The total scores range from 22 to 132 and the sub-scores are calculated as sums of selected questions.[25,26]

Statistical analyses

Categorical variables are reported as percentage distributions and numerical data as medians with quartiles. Age was assessed with years and months and changed to decimal numbers. Chi square test and Fisher's exact test were used for comparisons between the three villous atrophy groups in categorical variables and Kruskal-Wallis test in quantitative variables. The groups were adjusted with the years of birth and diagnosis, age, and gender using binary logistic regression. P value ≤ 0.05 was considered significant. Statistical analyses were performed with SPSS version 25 (IBM Corporation, Armonk, New York).

Study ethics

The research protocol was approved by the Regional Ethics Committee of the Pirkanmaa Hospital District and by the Department of Pediatrics, Tampere University Hospital. The study follows the ethical guidelines of the 1975 Declaration of Helsinki. All patients participating in the supplementary interviews or answering the questionnaires provided written informed consent.

Results

Disease characteristics at diagnosis in childhood

Of 906 pediatric celiac disease patients included, three were diagnosed before the year 1970; 52 in 1970–1979; 85 in 1980–1989; 130 in 1990–1999; 407 in 2000–2009; and 229 in 2010–2014. Of all patients, 34% had PVA, 40% SVA, and 26% TVA at diagnosis. Children with TVA had more often extra-intestinal presentation, growth disturbances, and anemia at diagnosis, whereas abdominal pain and being screen-detected were less common compared to patients with less severe villous atrophy.

(Table 1) Patients with different severity of villous atrophy did not differ significantly in the frequency of other presenting symptoms. (Table 1)

Children with more advanced villous atrophy were born and diagnosed during earlier years of the observation period, whereas there was no difference in age at diagnosis. (Table 2) Severe villous atrophy was associated with shorter height, lower BMI, lower hemoglobin levels, and higher EmA and TG2ab values at diagnosis. (Table 2) The three villous atrophy groups were comparable in gender distribution (girls 63% in all groups), family history of celiac disease (41% vs. 50% vs. 43%, p=0.204), and severity of symptoms (data not shown).

Disease characteristics in adulthood

Altogether 212 (42%) of the 503 invited adult patients diagnosed in childhood completed the questionnaires a median of 18.1 (interquartile range 12.5, 30.6) yrs after the diagnosis. According to medical record data, responders were more often women (68% vs. 53%, p<0.001) and relatives of celiac disease patients (56% vs. 41%, p=0.009), and had less type 1 diabetes (7% vs. 14%, p=0.018) than non-responders. They were also diagnosed earlier (1998 vs. 2000, p=0.034). There was no difference between the groups in age at diagnosis or current age, or degree of mucosal damage, clinical presentation, growth parameters, hemoglobin levels, and celiac disease serology (data not shown).

Adult patients presenting with PVA and SVA at diagnosis in childhood were currently younger than those with TVA (median age 25.3 yrs vs. 26.6 yrs vs. 34.2 yrs respectively, p<0.001), diagnosed during more recent yrs (median 2002 vs. 2000 vs. 1988, p<0.001), older at diagnosis (median age 11.6 yrs vs. 8.6 yrs vs. 7.4 yrs, p=0.021) and more often women (82% vs. 68% vs. 55%, p=0.004). The three villous atrophy groups were comparable in prevalence of comorbidities and celiac disease-related complications, self-reported persistent symptoms, general health, health-related concerns, adherence to gluten-free diet, and challenges with the diet (Table 3) and, after adjustment

for current age, year of diagnosis and gender, in median BMI (data not shown). The groups likewise did not differ in employment or student status, presence of offspring, membership of a celiac society, smoking status, regular physical exercise, and use of prescription medication (Supplementary table 1). Furthermore, there were no differences in presence or severity of current gastrointestinal symptoms evaluated by the GSRS or in self-perceived quality of life evaluated by PGWB (Supplementary table 2).

Discussion

Our main finding is that although severe villous atrophy is associated with severe clinical characteristics at celiac disease diagnosis in childhood, it does not predict poorer long-term health or treatment outcomes in adulthood. According to this finding, intestinal biopsy is not needed for prognostic reasons in children diagnosed with celiac disease.

We found more severe villous atrophy at diagnosis to be associated with higher occurrence of extra-intestinal presentation, including particularly anemia and growth disturbances, whereas the severity of atrophy was not associated with severity of gastrointestinal symptoms. The association between severity of villous atrophy and the presence of anemia and poor growth concurs with previous pediatric and adults studies by the present authors, Thomas et al. and Abu Daya et al.[17,27–30] As regards gastrointestinal or more "classic" symptoms, earlier pediatric studies by Dinler et al. from Turkey[11] and Semwal et al. from India[12] reported these to be associated with severe villous atrophy, whereas, in agreement with the present results, in studies conducted mainly in adults no such association has been observed.[30–33]

These somewhat inconsistent results could be explained by several factors. First, there were differences in the classification of the degree of mucosal damage. In the present study we classified lesion severity from PVA to TVA, these corresponding approximately to Marsh-Oberhuber grades 3a-c.[16] By contrast, most studies so far have applied either the Marsh classification dividing

small-bowel histology into three groups according to presence of intraepithelial lymphocytes (1), crypt hyperplasia (2), and villous atrophy (3), or the above-mentioned Marsh-Oberhuber classification,[12,30–32] introduced respectively in 1992 and 1999.[34,35] In addition, in the aforementioned adult study we used the more quantitative villous height-crypt depth ratio.[33] Note that, besides the grade of mucosal damage, the length of damage along the small intestine may also affect the clinical presentation[36], although this remains controversial.[37] Another explanation for the inconsistent results could be differences in study designs and classification of the phenotype. The latter is particularly challenging in celiac disease, in which patients may experience various symptoms simultaneously. Geographical factors may also play a role, as, for example, in India the classic presentation remains common[12,38], whereas in Western countries clinical features have gradually become milder and/or more atypical.[13,39,40] The heterogeneous presentation may also hamper the evaluation of statistical significance, especially in studies comprising a smaller number of patients.

Notably, notwithstanding the association between advanced villous atrophy and severe clinical characteristics at diagnosis in childhood, the severity of villous atrophy did not predict the presence of co-morbidities and complications in adulthood. To the best of our knowledge, this is the first study to evaluate this issue in celiac disease patients diagnosed in childhood. The current findings are in line with those of our adult study, in which we observed that, despite longer time required for full mucosal healing on a gluten-free diet, patients presenting with severe villous atrophy had a long-term prognosis equal to those with less severe damage.[8] Also, presence of villous atrophy compared to normal mucosal findings in a biopsy conducted at the time of diagnosis in patients with dermatitis herpetiformis, cutaneous manifestation of celiac disease, did not affect long-term health outcomes.[41] Somewhat alarmingly, Elfström et al. reported the degree of histopathologic changes at diagnosis to be associated with an increased risk of lymphoproliferative malignancy in adults.[10] However, it must be realized that the authors compared individuals with Marsh 3 lesion to those with less severe Marsh 0-2 damage, which indicates possibly in many cases non-celiac duodenal changes or completely

normal mucosa. By contrast, the ESPGHAN criteria[4] are based on evidence that almost all children fulfilling the serological criteria have morphological changes parallel to those studied here.

Besides the complications and co-morbidities, severity of villous atrophy at diagnosis in childhood did not predict long-term symptoms or self-perceived health and quality of life in adulthood. In our earlier adult study, long duration and severe symptoms before the celiac disease diagnosis predisposed to persistent symptoms on a strict gluten-free diet.[9] However, the effect of the degree of histological damage at diagnosis was not studied and, as already mentioned, the correlation between symptoms and histology seems to be weak.[30–33] It is therefore likely that even in adults symptom persistence reflects mostly other than initial histology-related factors.[42] However, re-biopsy should be considered with a low threshold in those with persistent symptoms as especially "atypical" symptoms may associate with villous atrophy.[43] The lack of long-term significance of histological changes at diagnosis in childhood observed here supports this conclusion, particularly as children also usually have shorter diagnostic delay[44] and faster recovery of the mucosal damage than adults.[45] Finally, in spite of the rather small number of studies, current evidence does not suggest that children should undergo routine endoscopy to exclude other possible relevant pathological changes when celiac disease is diagnosed serologically.[3]

The main strengths of our study are the large cohort of children with confirmed celiac disease diagnosis and the wide variety of clinical and laboratory parameters collected at the time of diagnosis. In addition, grading of the mucosal pathology was based on a systematic histological assessment of several well-oriented duodenal biopsies for the whole study period. As a limitation, the earliest samples were obtained with a different technique and, although there is standardized training in our country and pathologist specialized in alimentary tract can be effortlessly consulted, the fact that subjective histological evaluation was done by many readers inevitably affects the results. Another limitation is that, despite the median follow-up time of almost 20 years, most of the responders are still quite young, given that complications of celiac disease often manifest at later age.

Also, the only moderate response rate of 42% among adult patients diagnosed in childhood could predispose to selection bias. Then again, the responders and non-responders were comparable in most of the patient record data, including distribution of severity of villous atrophy. The use of self-reported adulthood follow-up data could also be considered a limitation, particularly in the assessment of co-morbidities, but the use of validated questionnaires to evaluate current symptoms and quality of life improves the comparability of the results.[9,14,46] Finally, the necessity to use older histological classification applied during the entire study period instead of later introduced Marsh grading hampers the comparisons between this and other studies.

To conclude, although we found severe villous atrophy at diagnosis in childhood to be associated with more severe clinical presentation, it appears to have no effect on long-term health and treatment outcomes. These findings provide further evidence that biopsy is not essential in children with serologically confirmed diagnosis. Moreover, sharing the information about good prognosis of pediatric celiac disease with the families could prevent unnecessary concerns associated with severe histological and clinical presentation.

References

1. Singh P, Arora A, Strand TA, et al. Global prevalence of celiac disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2018;16:823-36.

2. Husby S, Koletzko S, Korponay-Szabó IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr*. 2012;54:136-160.

3. Husby S, Koletzko S, Korponay-Szabo I, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition guidelines for diagnosing coeliac disease 2020. *J Pediatr Gastroenterol Nutr*. 2019. Doi: 10.1097/MPG.0000000000002497

4. Werkstetter KJ, Korponay-Szabó IR, Popp A, et al. Accuracy in diagnosis of celiac disease without biopsies in clinical practice. *Gastroenterology*. 2017;153:924-35.

5. Paul SP, Sandhu BK, Spray CH, et al. Evidence supporting serology-based pathway for diagnosing celiac disease in asymptomatic children from high-risk groups. *J Pediatr Gastroenterol Nutr*. 2018;66:641-4.

6. Elitsur Y, Sigman T, Watkins R, et al. Tissue transglutaminase levels are not sufficient to diagnose celiac disease in North American practices without intestinal biopsies. *Dig Dis Sci*. 2017;62:175-9.

7. Koletzko S, Auricchio R, Dolinsek J, et al. No need for routine endoscopy in children with celiac disease on a gluten-free diet. *J Pediatr Gastroenterol Nutr*. 2017;65:267-9.

8. Pekki H, Kurppa K, Mäki M, et al. Predictors and significance of incomplete mucosal recovery in celiac disease after 1 year on a gluten-free diet. *Am J Gastroenterol*. 2015;110:1078-85.

9. Paarlahti P, Kurppa K, Ukkola A, et al. Predictors of persistent symptoms and reduced quality of life in treated coeliac disease patients: a large cross-sectional study. *BMC Gastroenterol*. 2013;13:75.

10. Elfstrom P, Granath F, Ekstrom Smedby K, et al. Risk of lymphoproliferative malignancy in relation to small intestinal histopathology among patients with celiac disease. *JNCI J Natl Cancer Inst*. 2011;103:436-44.

11. Dinler G, Atalay E, Kalaycı AG. Celiac disease in 87 children with typical and atypical symptoms in Black Sea region of Turkey. *World J Pediatr*. 2009;5:282-6.

12. Semwal P, Gupta RK, Sharma R, et al. Comparison of endoscopic and histological findings between typical and atypical celiac disease in children. *Pediatr Gastroenterol Hepatol Nutr*. 2018;21:86-92.

13. Kivelä L, Kaukinen K, Lähdeaho M-L, et al. Presentation of celiac disease in Finnish children is no longer changing: a 50-year perspective. *J Pediatr*. 2015;167:1109-15.

14. Kivelä L, Popp A, Arvola T, et al. Long-term health and treatment outcomes in adult coeliac disease patients diagnosed by screening in childhood. *United Eur Gastroenterol J*. 2018;6:1-10.

15. Taavela J, Koskinen O, Huhtala H, et al. Validation of morphometric analyses of small-intestinal biopsy readouts in celiac disease. *PLoS One*. 2013;8:1-8.

16. Dickson BC, Streutker CJ, Chetty R. Coeliac disease: an update for pathologists. *J Clin Pathol*. 2006;59:1008-16.

17. Nurminen S, Kivelä L, Taavela J, et al. Factors associated with growth disturbance at celiac disease diagnosis in children: a retrospective cohort study. *BMC Gastroenterol*. 2015;15:125.

18. Saari A, Harju S, Mäkitie O, et al. Systematic growth monitoring for the early detection of celiac disease in children. *JAMA Pediatr*. 2015;169:e1525.

19. Ladinser B, Rossipal E, Pittschieler K. Endomysium antibodies in coeliac disease: an improved method. *Gut*. 1994;35:776-8.

20. Hill ID. What are the sensitivity and specificity of serologic tests for celiac disease? Do sensitivity and specificity vary in different populations? *Gastroenterology*. 2005;128:25-32.

21. Leinonen H, Kivelä L, Lähdeaho M-L, et al. Daily life restrictions are common and associated with health concerns and dietary challenges in adult celiac disease patients diagnosed in childhood. *Nutrients*. 2019;11:1-10.

22. Revicki DA, Wood M, Wiklund I, et al. Reliability and validity of the Gastrointestinal Symptom Rating Scale in patients with gastroesophageal reflux disease. *Qual Life Res*. 1998;7:75-83.

23. Hutchings HA, Cheung W-Y, Russell IT, et al. Psychometric development of the Gastrointestinal Symptom Rating Questionnaire (GSRQ) demonstrated good validity. *J Clin Epidemiol*. 2015;68:1176-83.

24. Svedlund J, Sjödin I, Dotevall G. GSRS--a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Dig Dis Sci*. 1988;33:129-134.

25. Dimenäs E, Carlsson G, Glise H, et al. Relevance of norm values as part of the documentation of quality of life instruments for use in upper gastrointestinal disease. *Scand J Gastroenterol Suppl*. 1996;221:8-13.

26. Wenger NK, Mattson ME, Furberg CD, et al. Assessment of quality of life in clinical trials of cardiovascular therapies. *Am J Cardiol*. 1984;54:908-13.

27. Rajalahti T, Repo M, Kivelä L, et al. Anemia in pediatric celiac disease: association with clinical and histological features and response to gluten-free diet. *J Pediatr Gastroenterol Nutr*. 2016;64:1-6.

28. Nurminen S, Kivelä L, Huhtala H, et al. Extraintestinal manifestations were common in children with coeliac disease and were more prevalent in patients with more severe clinical and histological presentation. *Acta Paediatr*. 2019;108:681-7.

29. Abu Daya H, Lebwohl B, Lewis SK, et al. Celiac disease patients presenting with anemia have more severe disease than those presenting with diarrhea. *Clin Gastroenterol Hepatol*. 2013;11:1472-7.

30. Thomas HJ, Ahmad T, Rajaguru C, et al. Contribution of histological, serological, and genetic factors to the clinical heterogeneity of adult-onset coeliac disease. *Scand J Gastroenterol*. 2009;44:1076-83.

31. Dorn SD, Hernandez L, Minaya MT, et al. Psychosocial factors are more important than disease activity in determining gastrointestinal symptoms and health status in adults at a celiac disease referral center. *Dig Dis Sci*. 2010;55:3154-63.

32. Brar P, Kwon GY, Egbuna II, et al. Lack of correlation of degree of villous atrophy with severity of clinical presentation of coeliac disease. *Dig Liver Dis*. 2007;39:26-9.

33. Taavela J, Kurppa K, Collin P, et al. Degree of damage to the small bowel and serum antibody titers correlate with clinical presentation of patients with celiac disease. *Clin Gastroenterol Hepatol*. 2013;11:166-71

34. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue').

Gastroenterology. 1992;102:330-54.

35. Oberhuber G, Granditsch G, Vogelsang H. The histopathology of coeliac disease. *Eur J Gastroenterol Hepatol*. 1999;11:1185-94.

36. Weizman Z, Ben-Zion YZ, Binsztok M, et al. Correlation of clinical characteristics and small bowel histopathology in celiac disease. *J Pediatr Gastroenterol Nutr*. 1997;24:555-8.

37. Murray J, Rubio-Tapia A, Van Dyke C, et al. Mucosal atrophy in celiac disease: extent of involvement, correlation with clinical presentation, and response to treatment. *Clin Gastroenterol Hepatol*. 2008;6:186-93.

38. Poddar U, Thapa BR, Singh K. Clinical features of celiac disease in Indian children: are they different from the West? *J Pediatr Gastroenterol Nutr*. 2006;43:313-7.

39. Ravikumara M, Tuthill DP, Jenkins HR. The changing clinical presentation of coeliac disease. *Arch Dis Child*. 2006;91:969-71.

40. McGowan KE, Castiglione DA, Butzner JD. The changing face of childhood celiac disease in North America: impact of serological testing. *Pediatrics*. 2009;124:1572-8.

41. Mansikka E, Hervonen K, Kaukinen K, et al. Prognosis of dermatitis herpetiformis patients with and without villous atrophy at diagnosis. *Nutrients*. 2018;10:641.

42. Laurikka P, Kaukinen K, Kurppa K. Unravelling the mechanisms behind the persistent gastrointestinal symptoms in celiac disease – how can they lead to better treatment outcomes? *Expert Rev Gastroenterol Hepatol*. 2017;11:605-7.

43. Carroccio A, Ambrosiano G, Di Prima L, et al. Clinical symptoms in celiac patients on a gluten-free diet. Scand J Gastroenterol 2008;43:1315-21.

44. Riznik P, De Leo L, Dolinsek J, et al. Diagnostic delays in children with coeliac disease in the Central European region. *J Pediatr Gastroenterol Nutr*. 2019;69:443-8.

45. Bannister EG, Cameron DJ, Ng J, et al. Can celiac serology alone be used as a marker of duodenal mucosal recovery in children with celiac disease on a gluten-free diet? *Am J Gastroenterol*. 2014;109:1478-83.

46. Ilus T, Lähdeaho ML, Salmi T, et al. Persistent duodenal intraepithelial lymphocytosis despite a long-term strict gluten-free diet in celiac disease. *Am J Gastroenterol*. 2012;107:1563-9.

Figure legends

Figure 1. Flowchart of the study.

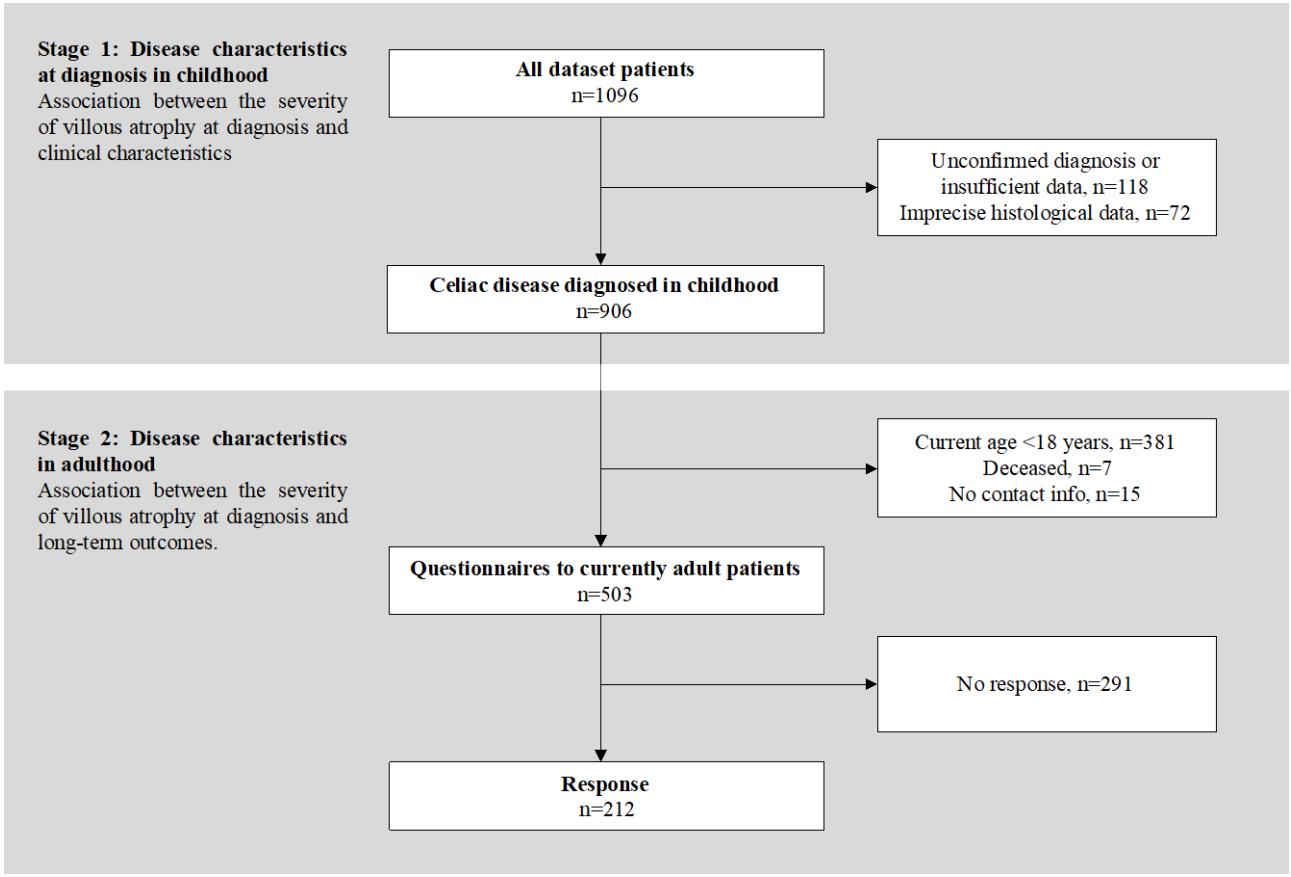

Table 1. Clinical characteristics in pediatric celiac disease patients with partial (PVA, n=306), subtotal (SVA, n=363) and total (TVA, n=237) villous atrophy at diagnosis.

	%	OR (95%CI)	P value	Adjusted OR (95%CI)[1]	Adjusted P value[1]
Gastrointestinal presentation					
PVA	51	1			
SVA	46	0.85 (0.62, 1.15)	0.284	-	-
TVA	47	0.88 (0.63, 1.25)	0.480	-	-
Extra-intestinal presentation					
PVA	19	1		1	
SVA	29	1.75 (1.21, 2.53)	0.003	1.73 (1.19, 2.52)	0.004
TVA	36	2.37 (1.60, 3.51)	<0.001	2.25 (1.49, 3.39)	<0.001
Screen-detected					
PVA	30	1		1	
SVA	25	0.75 (0.53, 1.05)	0.095	0.79 (0.56, 1.13)	0.193
TVA	17	0.46 (0.30, 0.71)	<0.001	0.57 (0.37, 0.88)	0.010
Diarrhea					
PVA	37	1			
SVA	37	1.03 (0.73, 1.45)	0.877	-	-
TVA	43	1.28 (0.88, 1.85)	0.197	-	-
Constipation					
PVA	15	1			
SVA	15	0.97 (0.61, 1.56)	0.908	-	-
TVA	16	1.07 (0.64, 1.79)	0.788	-	-
Abdominal pain[2]					
PVA	57	1		1	
SVA	47	0.67 (0.48, 0.94)	0.019	0.74 (0.52, 1.03)	0.077
TVA	42	0.54 (0.37, 0.78)	0.001	0.65 (0.44, 0.96)	0.032
Vomiting					
PVA	5	1		1	
SVA	8	1.72 (0.84, 3.52)	0.140	1.29 (0.60, 2.76)	0.518
TVA	13	3.09 (1.52, 6.25)	0.002	1.58 (0.74, 3.41)	0.240
Poor growth					
PVA	21	1		1	
SVA	36	2.04 (1.41, 2.94)	<0.001	1.83 (1.25, 2.66)	0.002
TVA	54	4.30 (2.90, 6.36)	<0.001	3.23 (2.14, 4.86)	<0.001
Anemia					
PVA	15	1		1	
SVA	21	1.47 (0.95, 2.27)	0.081	1.42 (0.92, 2.20)	0.117
TVA	32	2.73 (1.76, 4.25)	<0.001	2.50 (1.58, 3.96)	<0.001

[1]Adjusted for the year of diagnosis and birth
Data were available for >85% of patients except in (n): [2]757/906.

Table 2. Demographic data and selected growth and laboratory parameters in pediatric celiac disease patients with different severity of villous atrophy at diagnosis.

	Severity of villous atrophy, n= 906			
	Partial, n=306	**Subtotal, n=363**	**Total, n=237**	
	Median (Q_1, Q_3)	Median (Q_1, Q_3)	Median (Q_1, Q_3)	P value
Demographic data				
Age, years	8.0 (4.8, 12.4)	7.8 (4.6, 11.7)	7.2 (3.8, 11.7)	0.090
Year of birth	1997 (1991, 2002)	1997 (1989, 2002)	1993 (1981, 2001)	<0.001
Year of diagnosis	2007 (2001, 2010)	2006 (1998, 2010)	2001 (1986, 2008)	<0.001
Measurements				
Height[1], SD	0.3 (-0.4, 0.9)	0.0 (-0.9, 1.0)	-0.5 (-1.2, 0.2)	<0.001[6]
BMI[2], kg/m^2	16.7 (15.3, 19.5)	16.2 (15.1 18.5)	16.0 (15.0, 17.1)	0.004[6]
EmA[3], titer	1:200 (1:50, 1:500)	1:500 (1:200, 1:2000)	1:1000 (1:200, 1:4000)	<0.001[6]
TG2ab[4], U/l	64 (18, 120)	120 (49, 120)	120 (49, 120)	<0.001[6]
Hemoglobin[5], g/l	126 (118,133)	124 (115, 132)	121 (110,132)	0.008[6]

Data were available for >85% of patients except in (n): [1]428, [2]560, [3]474, [4]453, [5]656.
[6]Differences remained statistically significant after adjusting with the birth and diagnosis years.
BMI, body mass index; EmA, endomysium antibodies; Q_1 and Q_3 lower and upper quartiles; SD, standard deviation; TG2ab, transglutaminase 2 antibodies.

Table 3. Frequency of coexisting chronic conditions and various health- and treatment related factors in adult celiac disease patients with different severity of villous atrophy at diagnosis in childhood.

	Severity of villous atrophy, n=212			
	Partial, n=67	**Subtotal, n=84**	**Total, n=61**	
	%	%	%	P value
Co-existing conditions				
Allergy	50	47	35	0.203
Autoimmune thyroid disease	12	10	10	0.869
Bone fractures	22	27	28	0.660
Malignancy[1]	2	3	2	1.000
Miscarriage(s)	3	10	7	0.249
Osteoporosis or osteopenia	3	4	0	0.387
Other gastrointestinal disease[2]	9	6	5	0.611
Type 1 diabetes	8	7	8	0.767
Ongoing celiac-related symptoms[3]	25	16	25	0.282
Experience of health				0.154
Excellent or good	90	81	77	
Moderate or poor	10	19	23	
Health concerns				0.195
Nonexistent or mild	90	79	80	
Moderate or severe	10	21	20	
Strict adherence to a gluten-free diet	73	83	79	0.331
Restrictions in daily life due to the diet	48	42	50	0.611

[1]E.g. Hodgkin's or non-Hodgkin's-lymphoma, breast and brain cancer; [2]E.g. irritable bowel syndrome, gastritis, inflammatory bowel diseases, [3]self-assessment.

Supplementary table 1. Demographic and socioeconomic characteristics and aspects of lifestyle in adult celiac disease patients with partial (PVA, n=67), subtotal (SVA, n=84) and total (TVA, n=61) villous atrophy at diagnosis in childhood.

	%	OR (95%CI)	P value	Adjusted OR (95%CI)[1]	Adjusted P value[1]
Working full-time					
PVA	47	1		1	
SVA	65	2.05 (0.97, 4.34)	0.060	-	-
TVA	73	3.38 (1.47, 7.78)	0.004	1.63 (0.62, 4.28)	0.320
Student					
PVA	43	1		1	
SVA	35	0.69 (0.36, 1.34)	0.272	-	-
TVA	23	0.36 (0.16, 0.78)	0.009	0.83 (0.29, 2.36)	0.728
One or more offspring					
PVA	38	1		1	
SVA	32	0.78 (0.39, 1.53)	0.464	-	-
TVA	57	2.36 (1.16, 4.82)	0.018	1.23 (0.52, 2.88)	0.640
Member of celiac society					
PVA	51	1			
SVA	51	0.99 (0.52, 1.89)	0.986	-	-
TVA	53	1.11 (0.55, 2.23)	0.771	-	-
Smoking, current or quit					
PVA	30	1			
SVA	24	0.74 (0.36, 1.54)	0.421	-	-
TVA	44	1.83 (0.88, 3.79)	0.105	-	-
Regular medication[2]					
PVA	40	1			
SVA	46	1.36 (0.69, 2.70)	0.376	-	-
TVA	38	0.91 (0.43, 1.90)	0.796	-	-
Regular physical exercise					
PVA	92	1			
SVA	93	1.01 (0.29, 3.47)	0.986	-	-
TVA	92	0.92 (0.25, 3.34)	0.897	-	-

[1]Adjusted for gender, current age and year of diagnosis.
[2]E.g. medication for hypertension and diabetes, anti-depressants and thyroxin, excluding contraception.

Supplementary table 2. Gastrointestinal symptoms and health-related quality of life in adult celiac disease patients with different severity of villous atrophy at diagnosis in childhood.

	Severity of villous atrophy, n=212			
	Partial, n=67	**Subtotal, n=84**	**Total, n=61**	
	Median (Q_1, Q_3)	Median (Q_1, Q_3)	Median (Q_1, Q_3)	P value
Gastrointestinal Symptom Rating Scale[1]				
Total	1.7 (1.5, 2.3)	1.9 (1.5, 2.3)	2.0 (1.4, 2.4)	0.602
Diarrhea	1.3 (1.0, 1.7)	1.3 (1.0, 2.0)	1.3 (1.0, 1.7)	0.631
Indigestion	2.3 (1.8, 3.0)	2.3 (1.8, 3.0)	2.5 (1.8, 3.3)	0.776
Constipation	1.3 (1.0, 2.0)	1.3 (1.0. 2.3)	1.7 (1.0, 2.3)	0.253
Pain	1.7 (1.3, 2.0)	2.0 (1.3, 2.7)	1.7 (1.3, 2.7)	0.122
Reflux	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.5 (1.0, 2.3)	0.719
Psychological General Well-being Index[2]				
Total	104 (97, 113)	107 (96, 115)	105 (89, 112)	0.563
Anxiety	24 (20, 27)	24 (21, 26)	24 (19, 26)	0.824
Depressive mood	17 (16, 18)	17 (15, 18)	16 (15, 18)	0.125
Positive well-being	18 (15, 19)	18 (16, 20)	17 (14, 19)	0.178
Self-control	16 (14, 17)	16 (14, 17)	15 (14, 17)	0.401
General health	14 (12, 16)	14 (11, 16)	14 (12, 16)	0.700
Vitality	17 (16, 19)	18 (15, 19)	17 (13, 20)	0.892

Higher scores denote either [1]more severe symptoms or [2]better quality of life.