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Progression of celiac disease in children with antibodies against tissue transglutaminase and normal duodenal architecture

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Abstract: Celiac disease (CD) is a chronic autoimmune enteropathy triggered by gluten ingestion in genetically predisposed individuals. While the classic presentation involves intestinal damage, a subset of children presents with positive celiac-specific antibodies, particularly against tissue transglutaminase (tTG), but have normal or near-normal duodenal villous architecture upon biopsy. This condition is often referred to as potential celiac disease (PCD). Understanding the natural history and factors influencing the progression from PCD to overt CD (characterized by mucosal atrophy) is crucial for clinical management. This article synthesizes findings from recent studies to explore the progression of CD in children with positive tTG antibodies and initially normal duodenal architecture. It examines factors associated with progression, potential biomarkers, and current diagnostic and management approaches for this specific pediatric population.

Keywords: Celiac Disease, Tissue Transglutaminase Antibodies, Pediatric Gastroenterology, Duodenal Architecture, Antibody Testing, Pediatric Immunology, Gluten Sensitivity, Disease Progression, Gluten-Free Diet, Children's Health, Gastrointestinal Disorders, Intestinal Biopsy, Immune Response, Chronic Autoimmune Diseases, Serology Markers, Early Diagnosis.

Introduction: Celiac disease is a common condition affecting both children and adults, characterized by an immune response to gluten that leads to inflammation and damage in the small intestine (Abadie et al., 2024) [7]. The diagnosis typically relies on a combination of positive celiac-specific antibodies, such as anti-tissue transglutaminase (tTG) antibodies, and characteristic histological changes in duodenal biopsies, including villous atrophy (Marsh stage 3) (Auricchio et al., 2019) [1]. However, a significant number of children are identified with positive celiac serology but show no or minimal damage to the intestinal mucosa (Marsh stage 0 or 1) upon initial biopsy (Auricchio et al., 2019) [1]. This clinical scenario is often termed potential celiac disease (PCD) (Nemteanu et al., 2023) [6].

The trajectory of PCD in children is variable; some children may remain stable with positive antibodies but no mucosal damage, while others will progress to develop the characteristic villous atrophy of overt CD over time (Auricchio et al., 2019) [1]. The decision to implement a gluten-free diet (GFD) in children with PCD is a subject of ongoing debate and varies between clinical guidelines (Nemteanu et al., 2023) [6]. Predicting which children with PCD will progress to overt CD is a key challenge in pediatric gastroenterology (Piccialli et al., 2021) [14]. This article aims to review recent research on the progression of CD in children presenting with positive tTG antibodies and normal duodenal architecture, highlighting insights into predictive factors, diagnostic strategies, and potential future directions.

METHODS

This article is based on a narrative review and synthesis of the provided scientific literature focusing on the progression of celiac disease in children, particularly those with positive serology and normal duodenal architecture. The included references consist of original research articles, review articles, and conference abstracts published between 2019 and 2024.

The approach involved reviewing each provided reference to identify key findings, methodologies, and conclusions related to:

1. The definition and characteristics of potential celiac disease in children.
2. The rate and factors associated with the progression from potential to overt celiac disease.
3. The role of celiac-specific antibodies (especially tTG) in predicting progression.
4. The significance of duodenal histology in the context of positive serology.
5. The exploration of potential biomarkers for predicting mucosal lesion progression.
6. Diagnostic approaches and management strategies for children with positive serology and normal mucosa.

Information from these sources was synthesized to provide an overview of the current understanding of CD progression in this specific pediatric population. The findings and discussion presented are directly derived from the content of the provided references, with numerical citations used throughout the text to indicate the source of the information.

RESULTS

Studies have demonstrated that a substantial proportion of children with positive tTG antibodies and normal duodenal architecture at initial biopsy do progress to overt celiac disease over time (Auricchio et al., 2019) [1]. A retrospective cohort study observed the progression from PCD to CD in pediatric patients (Sakhuja & Holtz, 2021) [12]. The rate of progression can vary, and identifying factors that predict this progression is an active area of research.

Higher titers of tTG antibodies at diagnosis have been consistently associated with an increased risk of progression to mucosal atrophy (Auricchio et al., 2019) [1]. The dynamics of autoantibodies, including tTG, in pediatric CD and their relationship with age and disease progression are being investigated (Trovato et al., 2023) [8, 25].

While initial duodenal architecture is normal, subtle changes or the presence of specific cellular markers in the intestinal epithelium might precede overt villous atrophy. Research is exploring intestinal cellular biomarkers that could indicate mucosal lesion progression in pediatric CD (Vitale et al., 2021) [9, 26]. New intraepithelial γδ T-lymphocyte markers are being investigated for their potential in classifying CD in duodenal biopsies (Popp et al., 2021) [24]. Molecular biomarkers are also being explored for their role in the past, present, and future diagnosis and understanding of CD (Ramírez-Sánchez et al., 2020) [17, 31].

Diagnostic approaches for children with positive serology and normal mucosa are evolving. While duodenal biopsy remains a key diagnostic tool, particularly in cases with high-titer serology, there are ongoing discussions and variations in biopsy policies between regions like Europe and North America (Badizadegan et al., 2020) [19]. Novel diagnostic tests, such as intestinal and blood lymphograms, are being explored (Roy et al., 2023) [4, 28]. Dual sugar absorption tests, using monosaccharides like rhamnose and mannitol, are also being evaluated for their utility in treatment-naïve children with CD (Holtz et al., 2022) [3, 27].

The management of children with PCD, specifically regarding the initiation of a GFD, remains a clinical challenge (Trovato et al., 2019) [15, 21]. The question of whether and when to implement a GFD in PCD is actively debated (Nemteanu et al., 2023) [6].

Research is also exploring the genetic and environmental factors that might influence the development and progression of CD autoimmunity. Studies are investigating associations between CD autoimmunity and factors like maternal tuberculosis and pediatric Helicobacter pylori infections in genetically predisposed birth cohorts (Gudeta et al., 2022) [10, 11]. The complex interplay of genes, gluten, and the immunopathogenesis of CD is a subject of ongoing research (Abadie et al., 2024) [7].

Predictive modeling, including the use of machine learning, is being explored to predict the outcome of potential celiac disease (Piccialli et al., 2021) [14]. Recent progress and recommendations on CD from working groups are contributing to a better understanding and management of the disease (Scherf et al., 2020) [16, 22]. The broader context of becoming and being celiac, with special considerations for childhood and adolescence, is also being addressed in recent reviews (Chang et al., 2022) [5, 29].

DISCUSSION

The progression of celiac disease in children with positive tTG antibodies and normal duodenal architecture represents a complex clinical scenario that requires careful consideration. The findings from the reviewed literature underscore that this group is at a significant risk of developing overt mucosal damage

over time (Auricchio et al., 2019) [1]. The variability in progression highlights the need for better predictive markers and individualized management strategies.

High tTG antibody titers appear to be a consistent indicator of increased risk of progression (Auricchio et al., 2019) [1]. However, relying solely on antibody levels may not be sufficient for accurate prediction, emphasizing the need for additional markers. The investigation into intestinal cellular biomarkers (Vitale et al., 2021) [9, 26] and new intraepithelial lymphocyte markers (Popp et al., 2021) [24] holds promise for identifying subtle changes in the duodenal mucosa that precede overt atrophy. These efforts align with the broader search for molecular biomarkers in CD (Ramírez-Sánchez et al., 2020) [17, 31].

The role of duodenal biopsy in children with positive serology but normal mucosa remains a point of discussion and clinical variation (Badizadegan et al., 2020) [19]. While some guidelines may advocate for biopsy in certain cases, the invasive nature of the procedure necessitates the exploration of less invasive or more accurate predictive tools. Novel diagnostic tests, such as lymphograms (Roy et al., 2023) [4, 28]) and refined absorption tests (Holtz et al., 2022) [3, 27], could potentially contribute to a more nuanced diagnostic approach in the future.

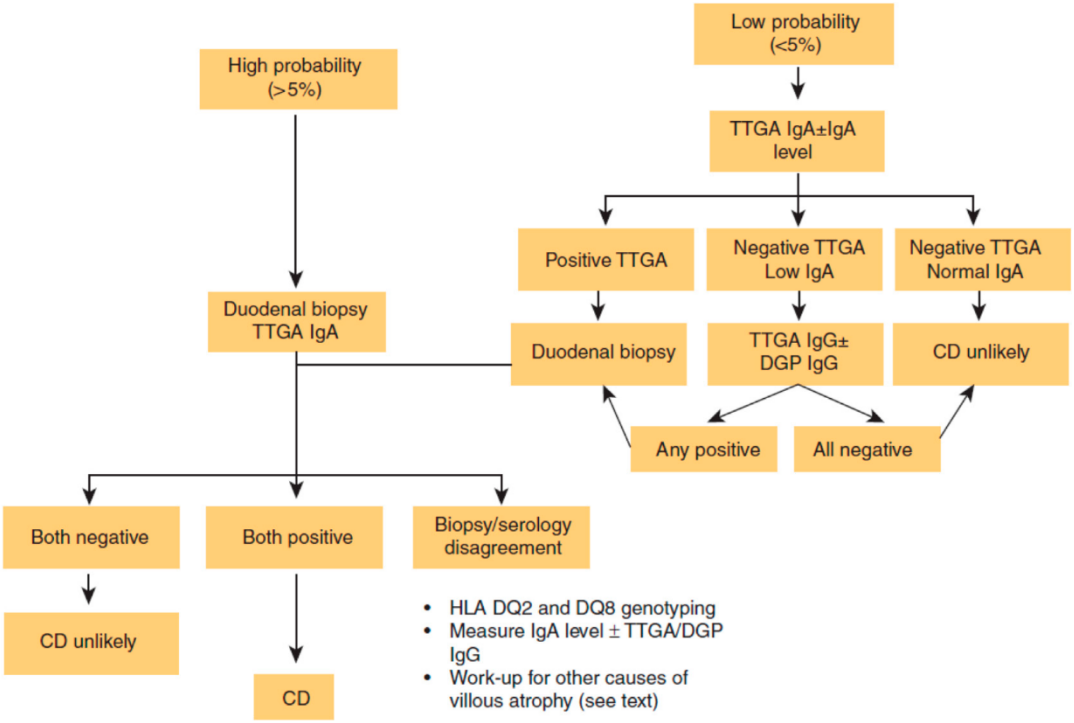

Fig. Celiac Disease: Diagnostic Standards and Dilemmas

The decision to initiate a GFD in children with PCD is challenging, balancing the potential benefits of preventing mucosal damage against the burden and social implications of a strict diet (Nemteanu et al., 2023) [6]; (Trovato et al., 2019) [15, 21]. More research is needed to determine the optimal management strategy for this group, potentially guided by improved predictive tools.

Understanding the interplay of genetic predisposition, environmental factors (Gudeta et al., 2022) [10, 11], and the immune response to gluten (Abadie et al., 2024) [7] is crucial for comprehending the mechanisms driving progression. Advances in precision medicine and machine learning offer exciting possibilities for integrating various data points to predict individual outcomes in PCD (Piccialli et al., 2021) [14].

CONCLUSION

In conclusion, the progression of celiac disease in children with positive tTG antibodies and normal duodenal architecture is a dynamic process. While serology provides an initial indication, predicting progression requires a deeper understanding of underlying biological mechanisms and the development of more precise biomarkers. Continued research into intestinal cellular changes, novel diagnostic methods, and predictive modeling is essential to refine diagnostic strategies and guide clinical management for this specific pediatric population, ultimately aiming to optimize outcomes and potentially prevent the development of overt celiac disease.

REFERENCES

Auricchio, R., Mandile, R., Del Vecchio, M. R., Scapaticci, S., Galatola, M., Maglio, M., Discepolo, V.,

Miele, E., Cielo, D., Troncone, R., & Greco, L. (2019). Progression of celiac disease in children with antibodies against tissue transglutaminase and normal duodenal architecture. *Gastroenterology, 157*(2), 413–420.e3. https://doi.org/10.1053/j.gastro.2019.04.004

Castillejo, G., Ochoa-Sangrador, C., Pérez-Solís, D., Cilleruelo, M. L., Donat, E., García-Burriel, J. I., Sánchez-Valverde, F., Garcia-Calatayud, S., Eizaguirre, F. J., Martinez-Ojinaga, E., Barros, P., Leis, R., Salazar, J. C., Barrio, J., Peña-Quintana, L., Luque, V., Polanco, I., Ribes, C., & Roman, E. (2023). Coeliac disease case-control study: Has the time come to explore beyond patients at risk? *Nutrients, 15*(5), 1267. https://doi.org/10.3390/nu15051267

Holtz, L. R., Hoffmann, J., Linneman, L., He, M., Smyrk, T. C., Liu, T. C., Shaikh, N., Rodriguez, C., Dyer, R. B., Singh, R. J., & Faubion, W. A. (2022). Rhamnose is superior to mannitol as a monosaccharide in the dual sugar absorption test: A prospective randomized study in children with treatment-naïve celiac disease. *Frontiers in Pediatrics, 10*, 874116. https://doi.org/10.3389/fped.2022.874116

Roy, G., Fernández-Bañares, F., Corzo, M., Gómez-Aguililla, S., García-Hoz, C., & Núñez, C. (2023). Intestinal and blood lymphograms as new diagnostic tests for celiac disease. *Frontiers in Immunology, 13*, 1081955.
https://doi.org/10.3389/fimmu.2022.1081955

Chang, D., O'Shea, D., Therrien, A., & Silvester, J. A. (2022). Becoming and being coeliac—Special considerations for childhood, adolescence and beyond. *Alimentary Pharmacology & Therapeutics, 56*(Suppl 1), S73–S85. https://doi.org/10.1111/apt.16851

Nemteanu, R., Clim, A., Hincu, C. E., Gheorghe, L., Ciortescu, I., Trifan, A., & Plesa, A. (2023). Is there a time and a place for the gluten-free diet in potential celiac disease? *Nutrients, 15*(18), 4064. https://doi.org/10.3390/nu15184064

Abadie, V., Han, A. S., Jabri, B., & Sollid, L. M. (2024). New insights on genes, gluten, and immunopathogenesis of celiac disease. *Gastroenterology, 167*(1), 4–22. https://doi.org/10.1053/j.gastro.2024.03.042

Trovato, C. M., Montuori, M., Leter, B., Laudadio, I., Russo, G., & Oliva, S. (2023). Role of age in dynamics of autoantibodies in pediatric celiac disease. *Italian Journal of Pediatrics, 49*(1), 38. https://doi.org/10.1186/s13052-023-01435-6

Vitale, S., Maglio, M., Picascia, S., Mottola, I., Miele, E., Troncone, R., Auricchio, R., & Gianfrani, C. (2021). Intestinal cellular biomarkers of mucosal lesion progression in pediatric celiac disease. *Pharmaceutics, 13*(11), 1971. https://doi.org/10.3390/pharmaceutics13111971

Gudeta, A. N., Andrén Aronsson, C., Binagdie, B. B., Girma, A., & Agardh, D. (2022). Incidence of celiac disease autoimmunity and associations with maternal tuberculosis and pediatric Helicobacter pylori infections in 4-year-old Ethiopian children followed up in an HLA genotyped birth cohort. *Frontiers in Pediatrics, 10*, 999287. https://doi.org/10.3389/fped.2022.999287

Sakhuja, S., & Holtz, L. R. (2021). Progression of pediatric celiac disease from potential celiac disease to celiac disease: A retrospective cohort study. *BMC Pediatrics, 21*(1), 149. https://doi.org/10.1186/s12887-021-02625-z

Auricchio, R., & Troncone, R. (2021). Can celiac disease be prevented? *Frontiers in Immunology, 12*, 672148. https://doi.org/10.3389/fimmu.2021.672148

Piccialli, F., Calabrò, F., Crisci, D., Cuomo, S., Prezioso, E., Mandile, R., Troncone, R., Greco, L., & Auricchio, R. (2021). Precision medicine and machine learning towards the prediction of the outcome of potential celiac disease. *Scientific Reports, 11*(1), 5683. https://doi.org/10.1038/s41598-021-84951-x

Trovato, C. M., Montuori, M., Valitutti, F., Leter, B., Cucchiara, S., & Oliva, S. (2019). The challenge of treatment in potential celiac disease. *Gastroenterology Research and Practice, 2019*, 8974751. https://doi.org/10.1155/2019/8974751

Scherf, K. A., Catassi, C., Chirdo, F., Ciclitira, P. J., Feighery, C., Gianfrani, C., Koning, F., Lundin, K. E. A., Schuppan, D., Smulders, M. J. M., Tranquet, O., Troncone, R., & Koehler, P. (2020). Recent progress and recommendations on celiac disease from the Working Group on Prolamin Analysis and Toxicity. *Frontiers in Nutrition, 7*, 29. https://doi.org/10.3389/fnut.2020.00029

Ramírez-Sánchez, A. D., Tan, I. L., Gonera-de Jong, B. C., Visschedijk, M. C., Jonkers, I., & Withoff, S. (2020). Molecular biomarkers for celiac disease: Past, present and future. *International Journal of Molecular Sciences, 21*(22), 8528. https://doi.org/10.3390/ijms21228528

[UEG Week 2020 Oral Presentations]. (2020). *United European Gastroenterology Journal, 8*(8_suppl), 8–142. https://doi.org/10.1177/2050640620927344

Badizadegan, K., Vanlandingham, D. M., Hampton, W., & Thompson, K. M. (2020). Value of biopsy in a cohort of children with high-titer celiac serologies: Observation of dynamic policy differences between Europe and North America. *BMC Health Services Research, 20*(1), 962. https://doi.org/10.1186/s12913-020-05815-0

Sandström, O., Norström, F., Carlsson, A., Högberg, L., van der Palz, M., Stenhammar, L., Webb, C., Ivarsson, A., & Myléus, A. (2022). Five-year follow-up of new cases after a coeliac disease mass screening. *Archives*

of Disease in Childhood, 107(6), 596–600. https://doi.org/10.1136/archdischild-2021-322755

Popp, A., Taavela, J., Graziano, P., Parente, P., Covelli, C., Lamacchia, C., Andriulli, A., Mäki, M., & Isola, J. (2021). A new intraepithelial γδ T-lymphocyte marker for celiac disease classification in formalin-fixed paraffin-embedded (FFPE) duodenal biopsies. *Digestive Diseases and Sciences, 66*(10), 3352–3358. https://doi.org/10.1007/s10620-020-06680-x