POTENTIAL COELIAC DISEASE

Riccardo Troncone

Principal investigator
Riccardo Troncone

Other components of the research group
Renata Auricchio
Luigi Greco
Roberta Mandile
Valentina Discepolo
Maria Maglio
Carmen Gianfrani

Background

The term potential celiac disease (PCD) has been coined to identify a subset of patients characterized by the presence of anti-tissue transglutaminase antibodies (anti-TG2) in the blood, but a normal intestinal architecture. From a clinical point of view PCD patients may be asymptomatic and may or may not evolve to a complete villous atrophy (VA). For this reason, clinical management of this condition remains still debated. The other main reason of interest of PCD resides in the fact it represents a unique model to investigate the natural history of CD as it allows to explore the steps that lead from the gluten specific adaptive T cell response to the full mucosal damage.

Main achievements

We prospectively enrolled 340 PCD children aged from 18 months to 18 years. Criteria for entry: at least two consecutive tests positive for anti-TG2 antibodies, confirmed by EMA IgA antibodies; normal or slightly infiltrated small bowel mucosa (Marsh stages 0- 1), HLA DQ2 or DQ8 positive haplotypes. Two hundred eighty of them were followed up on a gluten containing diet (GCD) up to 12.5 years. Antibodies and clinical conditions were checked every 6 months, while a duodenal biopsy was proposed every 2 years. Clinical, HLA and non HLA genes and histological data were combined in a multivariate analysis to predict villous atrophy at time of diagnosis. Over a median follow up time of 60 months (from 18 months to 12 years), 42/280 (15%) children developed VA while 89/280 (31.7%) stopped producing antibodies. Considering the length of follow up with censored data, the overall survival (remaining potential) of this cohort of children was 57% at 12 years. $\gamma\delta$ lymphocytes in the biopsy at diagnosis

were the best discriminators, followed by age and the individual genetic profile.
Recent findings have demonstrated the presence in the gut of subjects with PCD of Th1 cells reactive to gluten peptides, concomitantly with the existence of regulatory mechanisms that counteract the activation of inflammatory pathways destructive of mucosal epithelium. The lack of NK-mediated cytotoxic pattern in the gut of this peculiar group of patients has also been reported. Cytokine production of intestinal mucosa cells were analysed by qPCR and flow-cytometry in gut biopsies of children with overt- or potential-CD, and in healthy controls. Of note the lower expression of IL21 in PCD. Density of TCR$\gamma\delta$+ T cells was found markedly enhanced in intestinal mucosa of children with overt-CD compared to potential-CD or controls. By contrast, very few IL4+ T cells infiltrated the mucosa with villous atrophy compared to morphologically normal mucosa.

Future perspectives

The project is finalized to the characterization of the clinical, histological and immunological spectrum of potential coeliac disease. Special attention will be given to:

- Natural history of the condition. The follow-up of the present cohort will be prolonged.
- Identification of markers of the condition, in particular those predicting the evolution to villous atrophy.
- Identification of subgroups within the spectrum of PCD. Special attention to subjects in whom CD specific antibodies disappear from serum. The underlying immunological mechanisms involved will be investigated.
- Investigation of mechanisms leading to villous atrophy, in particular epithelial stress in relation to gliadin peptides, and activation of intraepithelial cytolitic response.
- Number and function of T regulatory cells.
- Comparison of intestinal microbiota composition between PCD, active CD and age matched controls.

Publications

1. *Tosco A, Salvati VM, Auricchio R, et al. Natural History of Potential Celiac Disease in Children. Clin Gastroenterol Hepatol. 2011; 9(4):320-325. doi:10.1016/j.cgh.2010.09.006.*
2. *Sperandeo MP, Tosco A, Izzo V, Tucci F, Troncone R, Auricchio R, Romanos J, Trynka G, Auricchio S, Jabri B, Greco L. Potential celiac patients: a model of celiac disease pathogenesis. PLoS One. 2011; 6;e21281.*
3. *Franzese A, Iafusco D, Spadaro R, Cavaliere O, Prisco F, Auricchio R, Troncone R, Valerio G, Study-Group on Diabetes of Italian Society of Pediatric Endocrinology and Diabetology. Potential celiac disease in type 1 diabetes: a multi center study. Diabetes Res Clin Pract 2011; 92:53-6.*

4. *Borrelli M, Salvati VM, Maglio M, Zanzi D, Ferrara K, Santagata S, Ponticelli D, Aitoro R, Mazzarella G, Lania G, Gianfrani C, Auricchio R, Troncone R. Immunoregulatory pathways are active in the small intestinal mucosa of patients with potential celiac disease. Am J Gastroenterol. 2013 Nov; 108(11):1775-84. doi: 10.1038/ajg.2013.303. Epub 2013 Sep 24.*

5. *Tosco A, Aitoro R, Auricchio R, Ponticelli D, Miele E, Paparo F, Greco L, Troncone R, Maglio M. Intestinal anti-tissue transglutaminase antibodies in potential coeliac disease. Clin Exp Immunol. 2013 Jan; 171(1):69-75. doi: 10.1111/j.1365-2249.2012.04673.x.*

6. *Auricchio R, Tosco A, Piccolo E, et al. Potential Celiac Children: 9-Year Follow-Up on a Gluten-Containing Diet. Am J Gastroenterol. 2014; 109(6):913-921. doi:10.1038/ajg.2014.77.*

7. *Borrelli M, Gianfrani C, Lania G, et al. In the Intestinal Mucosa of Children With Potential Celiac Disease IL-21 and IL-17A are Less Expressed than in the Active Disease. Am J Gastroenterol. 2016; 111: 134-44.*

8. *Mandile R, Discepolo V, Scapaticci S, et al. The Effect of Gluten-free Diet on Clinical Symptoms and the Intestinal Mucosa of Patients With Potential Celiac Disease. J Pediatr Gastroenterol Nutr. 2018; 66(4):654-656. doi:10.1097/MPG.0000000000001745.*

9. *Auricchio R, Mandile R, Del Vecchio MR, Scapaticci S, Galatola M, Maglio M, Discepolo V, Miele E, Cielo D, Troncone R, Greco L. Progression of Celiac Disease in Children With Antibodies Against Tissue Transglutaminase and Normal Duodenal Architecture. Gastroenterology. 2019 Aug; 157(2):413-420. e3. doi: 10.1053/j.gastro.2019.04.004. Epub 2019 Apr 9.*