COELIAC DISEASE (CLINICAL ASPECTS)

PROSPECTIVE COHORTS OF INFANTS AT RISK FOR CELIAC DISEASE

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Background

The etiology of CD is multifactorial as genetic, immunologic and environmental factors play a role in the development of the disease. CD is a very common disorder affecting approximately 1% in the general population, with higher prevalence in at-risk groups, first among all first degree relatives of patients (around 10%). The health burden of CD in terms of quality of life, complications, mortality, costs for treatment is noticeable, and prevention has become in the last decade one of the most important areas of research. Primary prevention strategies are based on one hand on the recognition of genetic factors underlying susceptibility and then of subjects primary target of the intervention, and on the other hand on the identification of environmental factors on which to intervene. A number of prospective studies have been recently produced in first-degree relatives to identify risk factors, and at least in two cases to test preventive strategies based on the timing of gluten introduction. The main results obtained have shown that cumulative prevalence in the first years of life (data from the Prevent CD project) of 6% and 13.5% at 3 and 5 years respectively. The main risk factors are, in particular, the HLA risk alleles dose (homozygous have around 30% of probability to develop celiac disease in the first 5 years of life) and female sex (almost double than male). No major risk is conferred by feeding practices in the first year of life, in particular, no protective effect by breastfeeding. Moreover, nowadays anti TG2 antibodies are the most highly predictive test for CD, while anti-deamidated gliadin

antibodies being not predictive.
However, further studies are still needed to render more solid data about natural history of the disease, to assess the contribution of other genetic and epigenetic factors, to clarify the role of microbioma/viroma changes in the period preceding the development of the disease, to clarify the role of environmental factors, first of all infectious agents, and finally also to find markers predictive of development of the disease (epigenetic changes, expression studies, metabolome, T cell markers).

Main achievements

We perfomed gene expression analysis of a set of 9 candidate genes, associated with CD, in 22 HLA predisposed children from at risk families for CD, followed from birth to 6 years of age. Nine of them developed CD (cases) and 13 did not (controls). We analysed gene expression at three different time points (age matched in the two groups): 4-19 months before diagnosis, at the time of CD diagnosis, and after at least one year of a gluten-free diet. At similar age points controls were also evaluated. Three genes (KIAA, TAGAP and SH2B3) were overexpressed in cases, compared to controls, at least 9 months before CD diagnosis. At a stepwise discriminant analysis, 4 genes (RGS1, TAGAP, TNFSF14 and SH2B3) differentiate cases from controls before serum antibodies production and clinical symptoms. Multivariate equation correctly classified CD from non-CD children in 95.5% of cases. The increasing incidence of celiac disease (CD) suggests that common infections before the onset of autoimmune diseases could be an important factor in switching the immune response. We explored also the relationship between early clinical events and the development of CD in genetically predisposed infants. 373 newborns from families with at least 1 relative with CD were recruited, and human leukocyte antigen DQ2- or DQ8-positive infants were followed up with clinical and serological evaluations, to determine the role of infections in the first years of life in increasing the risk of developing CD. An analysis of adverse events showed a higher frequency of respiratory tract infections among CD patients during the first 24 months of life. In a stepwise discriminant analysis, which included sex and human leukocyte antigen risk class, only respiratory infections in the second and first years of life significantly contributed to discrimination of case patients versus controls.

Future perspectives

A new cohort of 400 infants at risk of developing CD, because from families with already an affected member (parent or sibling), will be recruited in three years. The follow up will be till the age of 5 years. Expected prevalence of coeliac disease in this time is approximately 5-10%. Information about pregnancy and samples from

the mother (feces and blood) will be obtained. Enrolled children will be follow up from birth to 5 years of age periodically (at 5 months-before gluten introduction, and at 12, 18, 24, 36,48,60 months). During the observation period, information will be obtained about environmental of the house, diet, infections, therapy and any clinical relevant events reported by parents or family doctor. Growth parameters will be measured and serum, peripheral blood mononuclear cells, oral scrab, faeces and urine will be obtained. In the case of titres above the cut-off a small bowel biopsy for the diagnosis of CD will be offered.
Primary aim of this project is to identify risk factors, genetic and/or environmental (exposome), the latter with special emphasis on the prenatal period, associated with the development of the disease. Secondary aims are to relate these risk factors to metaboloma changes and to find predictive biomarkers of the development of the disease. Finally, we want also to describe microbioma changes in the period preceding the development of the disease at different time points up to 6 years of age.

Publications

1. *Auricchio R, Pedoto D, Troncone R. Novità in tema di celiachia: fattori di rischio, diagnosi e nuove strategie terapeutiche. Review. Prospettive in Pediatria. 2019; 49 (193): 25-34.*
2. *Hellmuth C, Uhl O, Demmelmair H, Grunewald M, Auricchio R, Castillejo G, Korponay-Szabo IR, Polanco I, Roca M, Vriezinga SL, Werkstetter KJ, Koletzko B, Mearin ML, Kirchberg FF. The impact of human breast milk components on the infant metabolism. PLoS One. 2018;13(6):e0197713. doi:10.1371/journal.pone.0197713. eCollection 2018.*
3. *Roca M, Vriezinga SL, Crespo-Escobar P, Auricchio R, Hervás D, Castillejo G, Mena MC, Polanco I, Troncone R, Mearin ML, Ribes-Koninckx C; PREVENT CD Study Group. Anti-gliadin antibodies in breast milk from celiac mothers on a gluten-free diet. Eur J Nutr. 2017 May 29. doi:10.1007/s00394-017-1476-1*
4. *Crespo-Escobar P, Mearin ML, Hervás D, Auricchio R, Castillejo G, Gyimesi J, Martinez-Ojinaga E, Werkstetter K, Vriezinga SL, Korponay-Szabo IR, Polanco I, Troncone R, Stoopman E, Kolaček S, Shamir R, Szajewska H, Koletzko S, Ribes-Koninckx C. The role of gluten consumption at an early age in celiac disease development: a further analysis of the prospective PreventCD cohort study. Am J Clin Nutr. 2017; 105(4):890-896.*
5. *Kirchberg FF, Werkstetter KJ, Uhl O, Auricchio R, Castillejo G, Korponay-Szabo IR, Polanco I, Ribes-Koninckx C, Vriezinga SL, Koletzko B, Mearin ML, Hellmuth C. Investigating the early metabolic fingerprint of celiac disease - a prospective approach. Autoimmun. 2016; 72:95-101.*
6. *Vriezinga SL, Auricchio R, Bravi E, Castillejo G, Chmielewska A, Crespo Escobar P, Kolaček S, Koletzko S, Korponay-Szabo IR, Mummert E, Polanco I, Putter H, Ribes-Koninckx C, Shamir R, Szajewska H, Werkstetter K, Greco L, Gyimesi J, Hartman C, Hogen Esch C, Hopman E, Ivarsson A, Koltai T, Koning F, Martinez-Ojinaga E, te Marvelde C, Pavic A, Romanos J, Stoopman E, Villanacci V, Wijmenga C, Troncone R, Mearin ML. Randomized feeding intervention in infants at high risk for celiac disease. N Engl J Med. 2014; 371(14):1304-15.*
7. *Galatola M, Izzo V, Cielo D, Morelli M, Gambino G, Zanzi D, Strisciuglio C, Sperandeo MP, Greco L, Auricchio R. Gene Expression Profile of Peripheral Blood Monocytes: A Step towards the Molecular Diagnosis of Celiac Disease? PLoS One. 2013; 8(9):e74747.*

8. *Hogen Esch CE, Rosén A, Auricchio R, Romanos J, Chmielewska A, Putter H, Ivarsson A, Szajewska H, Koning F, Wijmenga C, Troncone R, Mearin ML. The PreventCD Study design: towards new strategies for the prevention of coeliac disease. Eur J Gastroenterol Hepatol. 2010; 22(12):1424-1430.*

9. *Auricchio R, Cielo D, de Falco R, Galatola M, Bruno V, Malamisura B,Limongelli MG, Troncone R, Greco L. Respiratory Infections and the Risk of CeliacDisease. Pediatrics. 2017; 140(4).*

10. *Galatola M, Cielo D, Panico C, Stellato P, Malamisura B, Carbone L, Gianfrani C, Troncone R, Greco L, Auricchio R. Presymptomatic Diagnosis of Celiac Disease in Predisposed Children: The Role of Gene Expression Profile. J Pediatr Gastroenterol Nutr. 2017; 65(3):314-320.*