International Journal of Celiac Disease, 2017, Vol. 5, No. 1, xx
Available online at http://pubs.sciepub.com/ijcd/5/1/2

DOI:10.12691/ijcd-5-1-2

Screening for Celiac Disease in Rheumatology: HLA First?

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Abstract HLA genes have been shown to be strongly associated with a large repertoir of autoimmune diseases including Rheumatoid Arthritis (RA), Juvenile idiopathic arthritis (JIA) and Celiac Disease (CD). The present article will discuss what is the place of performing celiac disease associated serology in face of a rheumatologic patient, when gluten enteropaty is suspected. More specifically, should HLA be done prior to the serology? Unnecessary serial serological CD screening in such rheumatology patients could be avoided by performing an HLA typing, as a long-life marker of genetically CD-susceptible patients.

Keywords: *celiac disease, rheumatoid arthritis, juvenile rheumatoid arthritis, rheumatology, HLA*

Cite This Article: Hakim Rahmoune, Nada Boutrid, Mounira Amrane, and Belkacem Bioud, "Screening for Celiac Disease in Rheumatology: HLA First?" *International Journal of Celiac Disease*, vol. 5, no. 1 (2017): XX-XX. doi: xxxxxxxx.

1. Introduction

During the past decades, an accumulating evidence shows a dramatic rise in the frequency of autoimmune diseases, including Rheumatic (i.e. Rheumatoid Arthritis, RA) and gastrointestinal (i.e.Celiac Disease, CD) conditions [1].

Celiac disease, as an example of a well-described pathophysiological autoimmunity, is diagnosed via a myriad of laboratory tests discussed in recent guidelines from the European Society for Pediatric Gastroenterology, Hepatology and Nutrition, the American College of Gastroenterology and the World Gastroenterology Organisation: Immunoglobulin A anti-tissue transglutaminase (IgA-TTG) serology is thus considered as first-line test (as IgA-TTG greater than 10 times the upper limit of normal has a specificity and positive predictive value of 100%), while omiting intestinal biopsy for diagnosis is still controversial. The decreasing cost of HLA-typing may increase its use as a genetic background screening tool [2].

HLA genes are, in fact linked to a panel of autoimmune conditions by proven causative effects, the best known descriptions are CD and RA as well as Type 1 Diabetes [3].

Genes encoding human leukocyte antigen (HLA) are located in the major histocompatibility complex (MHC) on chromosome 6. Particualrly, HLA class II genomic region encodes the HLA-DR, HLA-DQ and HLA-DP proteins involved in presentation of peptides to HLA-class II-restricted CD4+ T-helper cells., and this region is associated with a large panel of autoimmune conditions [4].

2. HLA invlovment in Rheuamtoid Arthritis, Juvenile Idiopathic Arthritis and Celiac Disease

In both CD and RA, immune responses to modified protein antigens induce a loss of tolerance. In these two conditions, the antigen specific interaction between B and T cells is likely to drive an amplification loop, and lead to both T and B cell responses towards the target proteins involved [5]

RA and CD are also autoimmune diseases sharing a strong association with class II HLAs: individuals carrying HLA-DQ2.5 and/or HLA-DQ8 alleles present an increased risk of developing coeliac disease, whereas those carrying HLA-DR alleles have an increased risk of developing RA [6].

Juvenile idiopathic arthritis (JIA) are quite different and form a complex genetic trait influenced by both genetic and environmental factors. The International League of Associations for Rheumatology (ILAR) defined seven categories of JIA based on various clinical and laboratory findings, as JIA could be regarded as a myriad of autoimmune and non autoimmunes diseases appearing in pediatric ages: some children diagnosed as JIA do exhibit a non-autoimmune systemic form; namely the Still Disease or Systemic Onset JIA best classified as an auto-inflammatory syndrome [7 while the other subtypes of JIA seem to be effectively of autoimmune origine. [4,6]

Polyarticular Rheumatoid Factor- positive JIA, which can considered the childhood onset of seropositive adult rheumatoid arthritis, represents about 10% of all cases of

JIA, HLA DRB1 gene playing a major role in shaping RF-positive JIA in childhood similar to that seen in adults with RA. [4]

3. A Step Wised Serology/Genetic Appraoch

CD patients negative for any of these HLA alleles are very rare. Therefore, the absence of both HLA-DQ2 and HLA-DQ8 heterodimer makes diagnosis of celiac disease very unlikely (sensitivity >96 %). HLA typing of patients has been included as a useful test to exclude celiac disease in the ESPGHAN guidelines for CD diagnosis. [8,9]

HLA typing confers a high negative predictive value: patients with a negative HLA (i.e. neither DQ2 nor DQ8) will not develop CD; and a suggested strategy to avoid repeated CD screening would be to first perform an HLA test. [10]

Targetting the HLA risk first, rather than tracking positive serology, would be a rasonable step-up appraoch, probably cost efective and time saving: in the past, HLA typing has been expensive and time-consuming, but new single nucleotide polymorphisms techniques [11].

and other combined home-made procedures [12] have recently been reported as very cost-effective and work-time saving for HLA-DQ2 and DQ8 genotyping in CD screening.

In fact, a scottish study concluded that HLA typing would cost as high as £30,198, compared to a system of TTG IgA 3 yearly that costs £609 [13], but recent protocols decreased HLA typing prices from 2397.33 $ to 352.27$; and appear largely cost- effective versus serial serology [11,12].

In general population, the preferred test to screen for CD is the measurement of IgA TTG along with total serum IgA to avoid false-negative results due to selective IgA deficiency. Positive serology would lead to endoscopic small intestinal biopsies [14]. These serological tests, based on TTG associated to endomysial and deamidated gliadin peptides antibodies are recognized as performant screening tools. [15]

However, in asymptomatic members of a high-risk group, like those presenting RA, it seems reasonable to test first for negative result of HLA-DQ2/DQ8 in order to exclude CD, so that further serologic testing would be unnecessary [16]. Performing HLA genetic typings seems cost effective and could avoid subsequent fibroscopies and biopises [17]

Availability and health insurance coverage of such HLA analysis is questionable, specially in developing world; but recent studies emerging from the South Hemisphere confer solid arguments to such strategies [18] as CD is reported to be strongly associated with HLA-DQ2 in these regions [19].

4. Conclusion

HLA loci are long-life markers of genetically CD-susceptible patients before any clinical or serological signs, and thus increasingly considered to assess CD diagnosis.

Serogenetic screening without the requirement for follow-up small bowel biopsies provides a flexible, cost-effective methodology that could be widely applied to obtain accurate estimates of the prevalence of CD in large cohort studies

Conflict of Interest

None.

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