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Review Article

Risk of Addison's disease in patients with Celiac disease

Ilham Abd Allah Ali Al-Saleem

Department of Biology, College of Science, Al-Mosul University, Mosul, Iraq.

Correspondence: Ilham Abd Allah Ali Al-Saleem, Department of Biology, College of Science, Al-Mosul University, Mosul, Iraq. Email: ilhsbio41 @ uomosul.edu.iq.

ABSTRACT

Background: Celiac disease (CD) is an immune bowel defect in individuals have a genetic susceptible to gluten diets. CD may co-occur in individuals that may be suffer from other immune extra-bowel disturbance such as autoimmune-mediated endocrine disorders, like primary Addison's disease (AD) in which described by decrease the production or activity of adrenal gland hormones. The explanation of the association between these disorders propose that the steroid of adrenal gland , had convincing the onset of CD at the first time, and posteriorly hidden CD appearance .When AD onset and the serum steroid level reduced , the CD disease was appeared in full. Where is an immunogenetic background is one elucidation for the linkage between the two disorders in which the two heterodimers DQ8 and DQ2 that susceptible to CD, were cis-encoded and were respectively association imbalance with haplotype of ADD individuals (DRB1*04 and DRB1*03).

Keywords: Celiac disease, Addison's disease, Gluten-free diet, Steroid, HLA DQ2

Introduction

Addison's disease

Primary adrenal insufficiency (PAI) or (AD), is a scarce, possibility death and can treat . The large number status of autoimmune demolition of adrenal cortex give rise to (AD)[1-3]. (PAI) is a earnest pathologic disorder described by reduce output or activity of mineralocorticoids and adrenal androgen and/or glucocorticoids [4]. In spite of the fact that hypotension and hyperpigmentation are the most particular marker, bowel manifestations are popular and can be the first disorder of the individuals[5,6].This disease may be grouped as primary, secondary or tertiary, producing from infirmities influencing the cortex of adrenal gland[4]. In individuals at the beginning of their age, the disorder is widespread evenly in men and women [2]. PAI individuals are at higher risk of promote another autoimmune disorders**.** PAI detection is predominatingly go slow by several months. Because the disease is scarce, unto specialized doctors in the curative region scarcely supervise a small number of individuals. Presently, the proceedings for diagnosis, remediation and continuation of this uncommon disorder change considerably within Europe. The existence of 21-hydroxylase ((P450c21) auto-antibodies is the diagnosis of the popular autoimmune style of PAI [1,2,7] and distinguish of 21-hydroxylase in the zona glomerulosa of adrenal cortex, is a essential autoantigen in unknown reason of AD[8]. A study addressed the immunological and clinical lineaments of AAD by a cross-sectional, inhabitance -based research that involve 660 individuals with ADD from the Swedish Addison Registry from 2008 to 2014 and the cardiovascular risk factors was analyzed, 3594 peoples from the inhabitance -based study in Northern Sweden, MONICA (monitoring of trends and determinants of cardiovascular disease),render as healthy people. Precise surveillance of AAD individuals is guaranteed to disclose linked autoimmune disorders show that AAD individuals in Sweden did not have an elevated spread of hyperlipidemia , type 2 diabetes mellitus(DM), overweight or hypertension. The raised glucocorticoid commutation potions could be a risk factor for hypertension[9]. Another study addressed the heritability of AAD and detect the comorbidity of disease-

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related autoimmune through twins in Sweden. An inhabitance - based longitudinal cohort of 112,100 Swedish twins was employed to compute the heritability of AAD, and to reconnoiter co- appearance of autoimmune disturbance in ten organs of twin pairs with AAD. They specified 29 ADD twins. Of nine, five (5/9) was monozygotic and dizygotic was pairs zero out of fifteen (0/15) dizygotic couple were suitable for AAD. In monozygotic twin pairs autoimmune disorders styles influenced by AAD demonstrate a large grade of resemblance than dizygotic twins. AAD heritability was very elevated. Monozygotic twin harmony for redoubled autoimmune appearances propose robust genetic effect on disorder particulary in organ-specific [10].

AD is linked with the haplotypes DR4 (0404)-DQ8 and DR3-DQ2, especially high risk for disorder evolution is noticed when these appear in a heterozygous collection (DR4-DQ8/ DR3-DQ2) [2].

Celiac disease

(CD) is an autoimmune disturbance of small intestine [11-14]that evolves against grains gluten in genetically susceptible individuals[12-15] distinguished by exessive sensitivity to dietary gluten[16].Gluten protein is showed in particular grains, and occasions an autoimmune response in CD individuals [17] .CD acts on individuals of any sex or age[18]. The spread of CD worldwide is about 1% [19,20]. The essential remediation of(CD) is gluten-free diet (GFD)in which eliminate the gluten protein that gathering in grains for instance barley, triticale, rye and wheat [21-24] .The prolamin peptides in these grains give rise to painful ,chronic obliteration of microvilli of the epithelium of small bowel [25] and also can cause osteoporosis, abdominal distension ,chronic diarrhea, anemia, weight-loss due to malabsorption of nutrients if it left without treatment [25-27]and osteopenia in which decrease using up of milk and dairy products may have an important role in limitation low bone mass in CD individuals, in spite of no significant difference in exhaustion of milk between CD individuals and healthy people[28]. The best methods of the diagnosis of individuals with CD are the traditional diarrhea in prevailing and silent CD style. Those with silent CD have a reduction diarrhea, even though they have a normal symptoms of CD that involve anemia ,an irritable bowel syndrome, osteoporosis, malignancy or neurologic diseases[29]. In patients with a genetic susceptibility for the disease, the homozygous HLA DR3-DQ2[19,30,31], and /or HLA-DQ8[29,30] are together genotypes sensitive or important in evolution of CD disorder. [16,30-36]

Sensitivity to CD is robustly linked with special HLA class II alleles. And the evolution of CD is also linked with non HLA genetic agents. [37, 38]

Celiac disease and Addison's disease

Multiple autoimmune syndrome (MAS) are the three or more autoimmune disorders clarify in a single individual [39]. A large number of CD individuals at risk for MAS[40]in which the occurrence of CD in MAS individuals is increased from 10- to 30-fold although in a large volume of CD individuals occurrence are mute or clinically without symptomatic . CD-related autoimmune disturbances can be either particular to organ, for instance Hashimoto's thyroiditis and Type 1 diabetes mellitus (DM), or the autoimmune disturbances non particular to organ for instance scleroderma, Sjogren's syndrome ,systemic lupus erythematosus and rheumatoid arthritis [41] . CD repeatedly associated with a types of (MAS) which are extra-digestive appearance, and a systemic disorder rather than a disorder restricted to the bowel system and this made it returns to the category of autoimmune diseases[42].

A study show that one or several autoimmune disorders had evolved in 178 individuals, from 924 CD individuals retroactively recorded from 27 French adult gastroenterology and pediatric centers[40].

The researchers in a multicenter national study inspect the connection between the spread of autoimmune diseases in CD individuals and the duration of gluten consumption .For the early time the reports demonstrates that the increase the number of patients with autoimmune disorders in CD links to the duration of gluten consumption[43]. And other study showed that a GFD is important to prevent CD problems such as infertility ,anemia, and osteoporosis, may also be useful in prevent and remediation of the underlying endocrinological disorders [44,45]. The connection between CD and many autoimmune defects has been elucidated dividing of a public genetic agent[43]. Another study done on individuals with multiple endocrine defects, hypophysitis or alopecia, AD, associated with CD that are susceptible to autoimmune defects and analogous heredity are deem to be clarifications for these linkages [44]. Another study found that the raised spread of autoimmune disturbance is also high in first-grade relatives of CD individuals. The researchers announce that autoimmune disorders elevated six-times through relatives and a risk elevated increase with age. Mute CD was recognized in a parts of these relatives and the spread of autoimmune defect in these parts as contrast to first-grade relatives not influenced by CD was significantly elevated about 6.3 ratio and the study confirm that the CD individuals in first- grade relatives have an elevated risk of autoimmune disorders, probably regarding to undiagnosed and, consequently, untreated CD[46].

CD and primary AD may coexist specially in individuals with autoimmune polyglandular syndrome(APS), which are a scarce diseases that combination of two or more autoimmune endocrinological defect, involving type 1 DM , AD ,thyroiditis, primary gonadal failure or hypoparathyroidism, take place[42].

The (APS) with AD are categorized into two various subtypes, on various methods of inheritance and on the basis of characteristic styles of disease combination. Individuals with autoimmune Addison's disease (AAD) are at comparatively high risk for other endocrine defect or non-endocrine autoimmune disorders[47].

The hesitation DR4-DQ8 and DR3-DQ2 haplotypes had no significant differences in a neoteric article in a greatest cohorts widespread of individuals with isolated AD contrast to individuals with APS II[48].

In (APS) type 1 ,there was about 12.5% of CD cases, and in type 2 CD occur in four out of 60 (6.7%) cases [49].

Lately, CD has been found in approximately 10% of individuals with (AAD)[4] and CD showed in one out of 40 (1\40) approximately (2.5%) of the isolated AAD patients[47].

The cohabitation of CD and autoimmune endocrine disorder , has newly been described. A case of 23-year-old female have a (AAD), kariotypically normal automatic premature ovarian failure and hypothyroidism resulting from Hashimoto's thyroiditis. They investigate the serum IgA anti-endomysium antibodies (EmA) level. In the biopsy of jejunal ,the existence of total villous atrophy and the favorable of Em A let the recognize of CD. These individuals with a (GFD) show a remarkable clinical development through a gradual reduction of the requirement of adrenal and thyroid replacements treatments, in three month duration .The EMA level in serum turn into negative after six months and a total mucosal healing in new biopsy of jejunal found after twelve months. This condition confirmed the linkage between CD and (APS); the premature diagnosis of these conditions is important for the risk of disorder such as lymphoma if CD untreated and because CD give rise to the washout of replace hormonal remedy in autoimmune thyroid disorder individuals.[50]

Another study on CD patients showed an extremely risk of AD occurance . Thus ,they advice to screened for CD in patients with AD. [51].Of 41 individuals with AD screened, five (12.2%) had CD: The three were formerly recognize CD ,involving testing their biopsies, the two had positive IgA-(EMA) with a histological testing of biopsy gained in both cases without laboratory or clinical proof of malabsorption[52].

The risk for (PAI) is an amazing 11-times higher in CD individuals against non CD individuals, nevertheless the optimum risk is [53] ,in a research found that a twelve-year-old CD adolescent existing as acute adrenal insufficiency. A (GFD) had a curative function, where the large number of the symptoms and clinical marker of AD vanish in a small number of days [12].

While another study clarify that the GFD does not the change natural history of AAD by a study on seven patients were explained as having formerly specified AAD and CD at the onset of the article. Out of seven ,six individuals had CD and were take GFD before AAD. [51].

Chronic adrenal insufficiency is tricky to recognize. Typical problems involve generalized weakness ,chronic malaise and fatigue. Gastrointestinal appearance are existing in approximately fifty percent, which involve nausea ,lower abdominal cramps, anorexia and weight loss [6] amenorrhoea ,anaemia ,reduced bone mineral density, pigmentation [52].

Another study found that during treatment of three patients ,two individuals with dermatitis herpetiformis and AD and one with CD unaccompanied by the rash, but with AD and juvenile DM. The susceptible factors to the multiple endocrine conditions in these individuals with small bowel disorder and/or gluten-sensitive skin stayed unknown. Of three two individuals had HLA-B8, nobody was recognized to have influenced on relatives, and the AD noticed before, at the same time, or after the individuals contracted CD or dermatitis herpetiformis [54].

They recently suppose that there is an association between CD individuals especially with serum IgA low level and AD disease.[55]

In individuals with AAD there is a large spread of both IgA deficiency and CD. So, the testing of tissue transglutaminase autoantibodies(tTGAbs) of the IgA circulating levels and for IgA class and screening for CD is serious. Individuals with (AAD) are susceptible to evolve other autoimmune aspects . A raise spread of CD with AAD has newly been appeared in individuals of North Europe. Lack of IgA is the greatest repeatedly kind of immunodeficiency through people and is existing in approximately one in each six hundred persons in the people. IgA lack is popular in autoimmune disorder individuals, but information regarding to AAD are yet not present [49].

Immunogenetic background for the link between addison's and celiac disease:

AAD individuals commonly take corticosteroid remedy to right their reduction in adrenocortical. A study found that IgA-tTGAbs plus AAD individuals with a naturalistic infiltration of mucosa, the used of a large steroid surrogate remedy could decrease the infilteration of mucosa, so this lead to a incorrect negative estimate of biopsy of duodenal[49].

Another study describes CD in individuals ceasing chronic steroid treatment [56,57] and steroids have a well-identification curative function in the administration of refractory CD [58]. The technicalities by which steroids conserve the bowel mucosa contra injurious gluten influences are not obvious. In individuals with untreated and not identified CD, the steroids pharmacokinetics can be changed; particulary, those with decreased the binding of protein and raise magnitude of apportionment hypoalbuminaemia. Hypoalbuminaemia modification may require decreasing of steroids preservation potion [58].

A researchers found the reactivation of CD in individuals after the remediation of Cushing's disorder and occurrence of other defects specially autoimmune pathogenesis that characteristically have appear after a short time of surgical intrusion for Cushiug's disease. They have noticed failure of ovary, an autoimmune painless thyroiditis, a Lofren syndrome. They believe that high levels of steroid in the blood conserve against autoimmune diseases [57].

The HLA alleles are found in approximately 30-40% of normal individuals so its existence is important but not crucial [59]. The HLA typing is deemed by the new ESPGHAN guidelines a recognize device in CD. Class II HLA gives a lot of datum related to autoimmune pathology [60], which are in charge of about 40-50% of cases of Diabetes Mellitus(DM) [61]. There are susceptible to HLA sites in autoimmune disorders like HLA-DR B1 03 that keep safe against disorders (AD, DM). HLA-DR B1 07 were found in AD and DM. In addition to HLA DQ8, HLA

DQ2 risk about (90% of CD cases). Absence of HLA DQ2/DQ8 in CD individuals are scarce, act for approximately 5% of those recognized with CD [59,62].

Other articles found that the heterodimer (HLA)-DQ2 (A1*0501, B1*0201) found in approximately 90- 95% of CD persons [63-68],in addition to another style DQA1*03 and DQB1*0302 (DQ8)[63,64,69]. The hesitancy of the DQA1*0501 and DQB1*02 alleles in CD Turkish children was elevated comparatively to healthy children. The DQA1B1 (*0501; *0201) haplotype was existing in 46 from 55 CD individuals approximately 83.6% and in12 from 50 healthy children approximately 24%. The residual 9 CD children were carried the haplotype DQ8 (A1*03;*B10302) [70].

The inherited predisposing to (AAD) is robustly linked with HLA (DR4-DQ8) (DRB1*04, DQA1*03 and DQB1*0302) haplotype and\or DR3- DQ2 (DRB1*03, DQA1*0501 and DQB1*02) haplotype [2] where is another study found that the HLA DQA1*0501 genotype is significantly more popular in AD person about 70% than the healthy people about 43%[71].

Where is an analogous immunogenetic background is one clarification for the association between CD and AD disorders recognized by Betterle, et al in their individuals, the heterodimers susceptible to CD, DQ8 and DQ2, were cis-encoded and were in relationship to imbalance with DRB1*04 and DRB1*03. The haplotypes concerned with CD therefore involve the haplotypes susceptible to AAD[49].

Conclusion

Precocious recognition of CD disorder in greatly predisposed individuals may lead to the CD remediation and evolved hegemony of related disorders.

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