Epstien-Barr Virus may be Related to the Pathogenesis of Alopecia Areata

Thesis

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Introduction

Alopecia areata (AA) is a chronic inflammatory condition causing non-scarring hair loss. The lifetime risk of developing the condition has been estimated to be 1.7% with men and women being affected equally and it occurs in all racial groups. It may present at any age but is more common in children and younger adults ***(Mandani and Shapiro, 2000)***.

Severity of AA ranges from localized AA, which accounts for most cases, to total loss of scalp hair (alopecia totalis) (AT) or loss of all body hair (alopecia universalis) (AU) ***(Bertolino, 2000)***.

Although other autoimmune disorders sometimes occur with AA, most patients are healthy. Autoimmune thyroid disease and vitiligo considered the most important association with AA, and other autoimmune disorders are much less common ***(Hordinsky and Ericson, 2004; Seyrafi et al., 2005)***.

Approximately 20% of affected people have a family history of the disease, suggesting a genetic predisposition ***(McDonagh and Messenger, 1996; Blaumeiser et al., 2006)***. Discordance for AA in identical twins also suggests that an environmental trigger exists ***(Jackow et al., 1998)***. Associations have been reported with major histocompatibility complex (MHC), cytokines and immunoglobulin genes indicating a polygenic basis ***(Martinez-Mir et al., 2007)***.

Alopecia areata has an unpredictable course. Patients may present with several episodes of hair loss and hair regrowth during their lifetime. Recovery from hair loss may be complete, partial, or none. Patchy AA is usually self-limiting. Complete regrowth can be expected within one year in most patients, with or without treatment ***(Shapiro and Madani, 1999)***.

Treatment is not mandatory, since AA is benign and tends to remit spontaneously, and since treatment does not prevent recurrences. Nevertheless, because AA can cause extreme psychologic distress in young people, most physicians offer treatment. Current treatments include corticosteroids, minoxidil, anthralin, and contact sensitizers. Treatment of AA is intended to stimulate hair regrowth and reduce inflammation. Treatment has no effect on the natural course of AA. The choice of treatment plan depends on the age of the patient and the extent of scalp involvement ***(Dombrowski and Bergfeld, 2005)***.

Epstein Barr virus (EBV) is one of the most successful viruses, infecting over 90% of humans. It is a member in the herpes virus family. The herpes virus family is clustered into three subfamilies, α, β and γ herpesviridae, based on host cell range, site of latent infection cytopathology and duration of the reproductive cycle. Epstein Barr virus is a prototype of the γ herpesviridae, a subfamily characterized by tropism for B and T lymphocytes ***(Tosato et al., 1995)***.

Furthermore, EBV is closely related to viruses present in old world nonhuman primates, including EBV-like viruses of chimpanzees and rhesus monkeys. For example, the rhesus monkey virus and EBV share similar sequences and genetic organization, and they maintain persistent infection in the oropharynx and in B cells ***(Moghaddam et al., 1997)***. Thus, EBV probably evolved from a nonhuman-primate virus ***(Cohen, 2000)***.

Epstein Barr virus infection is usually asymptomatic in children. However, 30%–40% of adolescents who contract the virus will develop infectious mononucleosis ***(Fleisher et al., 1979)***.

After initial infection, the host becomes a lifelong carrier of EBV. In rare instances, EBV has been associated with several oncogenic presentations, including Burkitt lymphoma, posttransplantation lymphoproliferative disorders, lymphoma in human immune deficiency virus (HIV)-infected patients, and nasopharyngeal carcinoma ***(Smets and Sokal, 2002; Lopes et al., 2003)***. Furthermore, it has been suggested that EBV is associated with chronic fatigue syndrome, Hodgkin disease, and multiple sclerosis ***(kawa, 2000; Thacker et al., 2006)***.

Recently, researchers found that there was a sudden onset of AA in previously healthy young people, who self reported having infectious mononucleosis caused by EBV infection less than 6 months before the development of AA. Scientists considered EBV infection as a possible environmental trigger

factor for developing AA, where EBV infection was serologically confirmed for these patients and they recommend further investigation to prove this factor ***(Rodriguez and Devic, 2008; Rodriguez et al., 2010)***.

Aim of the Work

This work aims to study the possibility of EBV as an environmental trigger factor for alopecia areata in Egyptian patients.

Alopecia Areata

Epidemiology of Alopecia Areata:

Alopecia areata strikes all ages without gender predilection. Sixty percent of patients present with their first AA patch before 20 years of age. Onset before puberty tends to be associated with more extensive and resistant episodes of hair loss ***(McDonagh and Messenger, 1996)***. Thyroid disorders and vitiligo have the strongest relationship to AA. An incidence rate of 2.3% for thyroid disease has been reported in patients with AA. Vitiligo has been reported to occur in 4.1% of patients with AA. ***(Tan et al., 2002b; Wasserman et al., 2007)***.

There is equal distribution of incidence across races and sexes, as males and females are affected equally. The lifetime risk of AA has been calculated as approximately 1.7%, making it one of the most common autoimmune conditions. It accounts for 1% to 2% of new patients seen in dermatology clinics in the United Kingdom and United States. ***(Safavi et al., 1995; Garg and Messenger, 2009)***. In China, scientist reported an incidence of 3.8% and approximately 85.5% of the patients had their first episode before the age of 40 ***(Tan et al., 2002b; Wasserman et al., 2007)***.

The frequency of nail changes in AA patients ranges from 10% to 66% and nail pitting is the most common nail abnormality observed ***(Kasumagic-Halilovic and Prohic, 2009)***. The association between AA and atopy has been found

in more than 40% of AA patients ***(McDonagh and Tazi-Ahnini, 2002; Gilhar and Kalish, 2006)***.

Etiology and Pathogenesis of Alopecia Areata:

Alopecia areata is still an idiopathic disorder. Many factors were hypothesized to play a role in its pathogenesis, but genetic constitutions as well as non-specific immune and organ-specific autoimmune reactions have been the main areas of concentration ***(Madani and Shapiro, 2000)***.

A. Genetic Factors:

Many studies reveal the possibility that AA is a polygenic disease, with certain genes correlated with susceptibility and others with severity. Most likely, there is an interaction between genetic and environmental factors that trigger the disease ***(Du Vivier and Munro, 1975; Carter and Jegasothy, 1976; Tarlow et al., 1994)***.

In previous animal studies, it has been observed that the C3H/Hej mouse spontaneously develops an adult-onset form of AA-like disease that is very similar to human AA. Susceptibility intervals have been identified on chromosome 17 (Alaa1) and 9 (Alaa2) ***(Sundberg et al., 2003)***.

In 2004, Sundberg et al., identified two new intervals (Alaa3) located in chromosome 8 and (Alaa4) on chromosome 15. Many of the homologous human genes are located on human chromosomes 4 and 8. This data suggest that these

genes are involved with the susceptibility and progression of AA in the C3H/HeJ mouse model. ***In 1975, Du Vivier and Munro*** reported that, there is an association with chromosome 21 with increased incidence in Down's syndrome. A genome-wide scan identified additional loci that also are implicated in other hair disorders and psoriasis.

Alopecia areata is likely a complex polygenic trait that does not follow Mendel's laws ***(Shellow et al., 1992)***. Genetic studies found that 8.4% of the patients had a positive family history of AA, suggesting a polygenic additive mode of inheritance ***(Yang et al., 2004)***. Scientists reported four cases of congenital AA, which they followed for 5 years, suggesting that this disease can be classified as acquired or congenital ***(Lenane et al., 2005)***. In addition, there are reports of AA in twins, with concordance rate of up to 55% in identical twins ***(Scerri and Pace, 1992; Jackow et al., 1998)***.

B. Immunologic Factors:

Alopecia areata is classified as an autoimmune disease. Some researches points to a cell-mediated autoimmune mechanism as the underlying etiology of this disorder, although autoantibodies are presumed to play an integral role in the mechanism of AA ***(McDonagh and Messenger, 1996; McElwee, 1999)***. Evidence of autoantibodies to anagen stage hair follicle structures is found in affected humans and experimental mouse models ***(Tobin et al., 1997b; McElwee et al., 1998b)***.

It is proved that, AA has been linked with specific human leukocyte antigen (HLA) class II alleles (DQ3, DR4, DR6 and DR11) ***(Colombe et al., 1995; Duvic et al., 1995)*** with development of T cell repertoire centrally through the thymus that encompasses auto-reactive potential. Defective clonal deletion or anergy induction could lead to the accumulation of auto-reactive T cells in the peripheral sites such as lymph node, spleen, blood and skin. Although the specific auto-antigen(s) that could be presented by the antigen-presenting cells (APC) has/have not been identified yet, they are suggested to arise from the hair matrix, dermal papilla or during melanogenesis ***(Ohashi, 2002; Walker and Abbas, 2002)***.

Cytokines expression [interleukins (IL-1β, IL-2) and interferon (INF-γ)], cell mediated events, and target damage occur by either an antibody dependent cell-mediated cytotoxicity (ADCC) or direct CD8 cytotoxicity and perhaps through apoptotic pathways ***(Hoffmann et al., 1996; McElwee, 1999)***. The target organ of destruction in AA is the hair follicle, which is unique in that it undergoes a cycle of growth, differentiation and regeneration perpetually through the stages of anagen (sub-stages I-VI), catagen (sub-stages I-VIII), and telogen. Immunological events, possibly through cytokines interactions, alter the intricate communicative signals of the hair cycling to cause the deviation in the follicle dynamics. There is an arrest in follicle cycle at the anagen III to IV and pre-mature progression from early anagen to catagen, the stage of follicle regression, figure (1) ***(Alexis et al., 2004)***.

The antibody response to hair follicles in patients with AA has been found to be heterogeneous because different patients develop different patterns of antibodies to different hair follicle structures. The most common target structures were the outer root sheath, followed by the matrix, inner root sheath, and hair shaft ***(Tobin et al., 1997a)***.

Furthermore, there is an increased prevalence of antithyroid antibodies and thyroid microsomal antibodies in patients with AA ***(Wang et al., 1994)***. Scientists have shown an increased prevalence of gastric parietal cell antibodies as well as antinuclear and antismooth muscle antibodies in sera of patients with AA ***(Hordinsky et al., 1984; Kumar et al., 1995)***.

C. Cytokines:

The cytokines play a significant role in the pathogenesis of AA through mediating inflammation and regulating cell proliferation. Cytokines derived from epidermal keratinocytes as IL-1β and tumor necrosis factor-alpha (TNF- α) are potent inhibitors of hair follicle growth and in vitro produce changes in hair follicle morphology similar to those in AA ***(Philpott et al., 1996)***. An aberrant expression of cytokines of the TH1 type (INF-γ and IL-2) and IL-1β have been detected in the lesions of AA of the scalp and mediate the initiation of the immune response ***(Hoffmann et al., 1996; Gilhar et al., 2002)***.

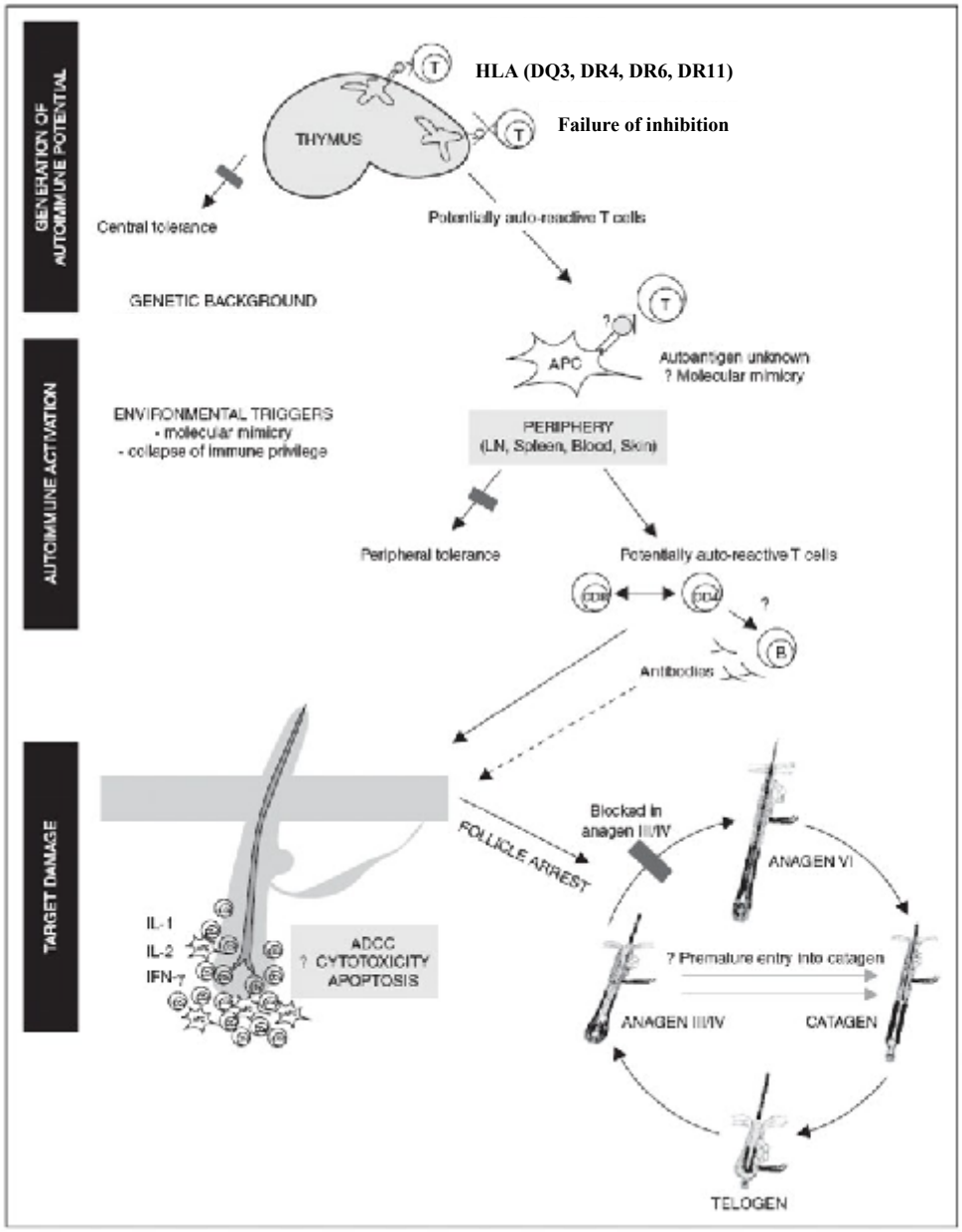

Figure (1): Illustration of the role of the immunologic factors and cytokines involved in the AA pathogenesis including autoimmune development, target damage and follicle cycle arrest. {Antibody dependent cell-mediated cytotoxicity (ADCC), Antigen presenting cells (APC), B lymphocytes (B), Cluster of differentiation (CD), Human leukocyte antigen (HLA), Interferon (IFN), Interleukin (IL), Lymph node (LN), T lymphocytes (T)} ***(Alexis et al., 2004)***.

D. Infections:

Alopecia areata is a complex disease where clinical presentation varies considerably between individuals. This fact reflects the mixed genetic background of the patients and the environment in which people live with random exposure to pathogens and toxic compounds ***(McElwee et al., 2003)***. Moreover, there is a possibility of infection to be a cause of AA either directly or as a consequence of a remote focus of infection ***(Messenger et al., 2010)***.

Scientists reported the possibility of cytomegalovirus (CMV) infection as they found the viral particles within the AA patches of scalp ***(Skinner et al., 1995)***. However, this has not been confirmed because other investigators have reported negative findings ***(Tosti et al., 1996; Jackow et al., 1998; McElwee et al., 1998a)***. The concept of molecular mimicry of the hair follicle with a virus is intriguing, but the evidence for a viral origin for AA is not conclusive ***(Madani and Shapiro, 2000)***. Recently, there is a study concerning the EBV as a possible trigger factor for AA ***(Rodriguez and Devic, 2008)***.

As regard the bacterial infections, recent evidence suggests that *Helicobacter pylori* infections play a role in the pathogenesis of AA and its eradication can improve the disease ***(Tuzun et al., 2010)***. Although other authors reported that, there is no causal link between *Helicobacter pylori* infection and AA ***(Abdel Hafez et al., 2009; Hernando-Harder et al., 2009)***.

Tooth extraction in patients with AA can improve the hair growth in those patients indicating that, the remote focus of dental infection can be one of causative factors of AA ***(Balcheva and Abadjiev, 2009)***. Moreover, scientists suggest that, there is an association between AA and the presence of bacterial pathogens in the oropharynx or history of immunization 6 month prior to occurrence of the disease. As they consider these factors as risk factors for development of the disease. The affected patients having less than 25% hair loss and the course of the disease in those patients less than 1 year ***(Morales-Sanchez et al., 2010)***.

E. Atopy:

Scientists observed that patients with a history of any form of atopy (atopic dermatitis, bronchial asthma or hay fever) have a 2-fold greater risk of having AA, and individuals with a history of atopic dermatitis specifically have a 70% increased risk of having AA. Patients with atopy are at 24% increased risk of having AT or AU rather than AA. Some researchers reported that, the risk of having any subtype of AA was almost double among those with a history of atopic dermatitis and the risk was almost 3 times greater for AT or AU. However, the mechanisms explaining an association among atopy and AA are not fully understood ***(Barahmani et al., 2009)***. Moreover, there was a correlation between the presence of atopy and the severity of AA ***(Shellow et al., 1992; Kasumagic-Halilovic and Prohic, 2008)***.

F. Emotional Stress:

Several studies suggest that stress may be a precipitating factor in some cases of AA ***(Baker, 1987)***. Higher prevalence of diagnosed psychiatric disorders have been reported in patients with AA ***(Colon et al., 1991; Ruiz-Doblado et al., 2003)***.It is apparent that AA causes dramatic and devastating emotions in patients, which can negatively impact their self-esteem, body image, and/or self-confidence ***(Tucker, 2009)***.

Other studies reported the possibility of the stress to activate the skin mast cells, which secreted vasoactive peptides, and cytokines that contributed to the inflammatory content of the perifollicular area ***(Fleisher et al., 1998)***. Furthermore, the skin mast cell activation and associated increased vascular permeability could be induced by intradermal administration of corticotropin-releasing hormones ***(Gupta et al., 1997)***. Accordingly, the use of corticotropin-releasing hormones receptor antagonists alone or together with mast cell blockers was suggested to be a therapeutic alternative in stress-induced AA ***(Katsarou-Katsari et al., 2001)***.

G. Other Factors:

1. Serum Ferritin Level:

Interestingly, it was found that the mean ferritin level in patients with AA was statistically significantly lower than in normal individuals without hair loss ***(Kantor et al., 2003)***.