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Review Article

Unraveling the Association of Multiple Sclerosis with Pregnancy, Cellular Immunity, and Alpha-Fetoprotein: A Historical Review and Immunity Analysis

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Abstract

The autoimmune disease of Multiple Sclerosis, also known as encephalomyelitis disseminated, is a chronic neurological disorder with autoantibodies directed against the insulating myelin sheath of the central nervous system nerve tracts. This autoimmune neuro-inflammatory disorder affects nearly 2 million people worldwide and is three-times more prevalent in women than men. Because MS is commonly found in women of childbearing age, this autoimmune disease occurs with some frequency during pregnancy. Because MS results in CNS inflammation and axonal degeneration, both the humoral and cell-mediated branches of the immune system are involved. Autoantibody production is induced against myelin basic protein, immune cell proliferation is initiated, and Th1 cytokine secretion ensues. Cell mediated expression of proteins in the MHC class II family, chemokines and their receptors, and FOX 3 transcription factors are also activated. Alpha-fetoprotein, which is known to participate in the remission of MS in pregnancy, is active in immune modulation of T-cell reactivity, antigen presentation, and increased expression of pro-apoptotic factors such as BAX, Bid, and others.

Keywords: alpha-fetoprotein; autoimmunity; multiple sclerosis; peptides; growth inhibitory peptide; gip; pregnancy; autoantibodies; cell immunity

1.Introduction

A) The Multiple Sclerosis Autoimmune Disease:

The autoimmune disorder of Multiple Sclerosis is a chronic inflammatory cellular immune disorder involving nerve damage in the central nervous system (CNS) (1). The cause of MS is not known but environmental factors and the Epstein- Barr virus are highly suspect and have been implicated (2,3). Immune dysregulation comprises the hallmark of MS resulting in immune cell infiltration into the CNS; this triggers demyelination, axonal damage, and ultimately neurodegeneration (4). Although the genetics of MS is not fully understood, involvement with family members with MS suggest a relationship to the HLA-DR15 haplotype as a factor of disease onset and progression.

B) Immune and Genetic Characteristics of Multiple Sclerosis

The MS disorder shares comorbidity with other autoimmune diseases such as diabetes, pernicious anemia, inflammatory bowel syndrome, and Hashomoto's thyroiditis which is the most common (5). Although MS is mildly inheritable, genetic studies have reported an increase of autoimmune MS in people with their first-degree relatives. Autoimmune cell proliferation during MS disease is mediated by memory B-cells in a HLA-DR haplotype-dependent manner. Depletion of B-cells employing therapeutic treatments in vivo can be accomplished using anti-CD20 antibodies which also served to reduce T-cell proliferation (6). In patients carrying the HLA-DR haplotype, peripheral Th1 cells generate proliferation of autoreactive $CD4^+$ T-cell reserves to increase their population. Thymus-derived T cells sensitized against myelin basic protein (MBP) self-antigens can secrete additional inflammatory mediators such as tumor necrosis factor (TNF), various cytokines, and prostaglandins (7). Together with MS autoantibodies, such inflammatory mediators act to strip away the myelin sheath insulation that contributes to axon destruction.

MS management can sometimes be beneficial using Vitamin-D and other vitamin supplementations, and applying dieting practices such as low fat intake, frequent fish meals, and intake of thiol antioxidants and anti-inflammatory omega-3 fatty acids. Gut absorption can be further aided by use of added digestive enzymes and probiotics (8). Finally, transdermal histamine and adenosine monophosphate applications may serve to benefit some MS patients.

II. Alpha-fetoprotein and Multiple Sclerosis (EAE):

Alpha-fetoprotein (AFP) is a gestational-age-dependent biomarker present in both fetal and maternal serum during pregnancy (9). AFP has a long history as an immunomodulatory agent associated with fetal growth and development. Regarding MS, recombinant human AFP has been reported to reduce (MS) EAE-induced neuroinflammation, to increase apoptosis of activated immune cells by inhibiting BCL-2 related pathways, and to increase the presence of FAS-related (CD95) ligands in apoptosis (10). Furthermore, AFP increased both FOXp3 transcription factor expression in lymph nodes and T-reg cell numbers in the CNS (11). AFP has been studied in animal models of MS and was found to both treat and prevent the induction of EAE. AFP exerts significant immunosuppressive effects

on T-cells in vitro at physiologic concentrations and has the capacity to induce suppressor T-cells (12,13). Overall, several investigators have shown a beneficial effect of AFP on the course of EAE (MS) in guinea pigs and several other animal models (13). During human pregnancy, maternal serum AFP levels gradually increases until the 30-32 week period of the third trimester; this is a gestational period in which more than 50% of MS patients experience disease remission (14). Thereafter, to term pregnancy, maternal serum AFP levels decrease to low nanogram/ml levels during postpartum when most MS relapses were found to occur.

III. Objectives of the Present Report:

The implementation of maternal serum, alpha fetoprotein (AFP) and placenta biomarker (MSOB) screening during pregnancy has become a standard of practice for obstetrical care in many countries worldwide. Since such screening results include serum levels and risk data information, seeking a role for such biomarkers in autoimmune associated pregnancies (i.e., Multiple Sclerosis (MS)) might provide further insight into treatment and management modalities in such populations. Thus, the primary objective of the present treatise is to take advantage of the fact that most pregnant women undergo second trimester maternal serum AFP screening to determine whether such AFP biomarker concentrations and medians are abnormal during Multiple Sclerosis autoimmune-associated pregnancies. The second objective is to examine whether AFP could influence the course of disease and affect treatment and management modalities. The third aim of the paper will attempt to shed light on whether the AFP molecule itself could contribute to disease remission by reducing the symptoms and unwanted manifestations of this autoimmune disease during pregnancy. It will be demonstrated in this report that the AFP polypeptide plays a significant role in MS remission during pregnancy by modulation of both the humoral and cellular immune systems.

Alpha-fetoprotein, Pregnancy, and Autoimmune Cellular Immunity:

MS is a Th-1 lymphocyte mediated autoimmune disease; during pregnancy, comprising a Th-1 to Th-2 expressing lymphocyte population shift occurs which provides an immunoprotective effect for the mother (7). An immunomodulatory effect of estriol therapy on cytokine profiles demonstrated that significant increases in IL-5 and IL-10 occurred concomitantly with decreased tumor necrosis factor (TNF) alpha levels (15). The increase in IL-5 was due to escalated number of $CD4^+$ and $CD8^+$ expressing T-cells, while increased IL-10 levels were attributed to expanded numbers of $CD64^+$ monocytes. The decreased TNF-alpha serum levels were caused by a reduction in numbers of $CD8^+$ T-cells (16).

AFP has been reported to produce remissions in multiple sclerosis (MS) patients during human pregnancy (17). Using recombinant human AFP (RHAFP) in animal models of EAE, RHAFP markedly improved the clinical manifestation of EAE by preventing CNS inflammation and axonal degeneration (18). In a prior study, T-cells from AFP-treated mice were shown to significantly reduced activity toward the myelin oligodendrocyte glycoprotein (MOG), a MS mediator and antigen; and this served to exhibit less T-cell proliferation and reduced TH1 cytokine secretion (19). In addition, AFP affected the humoral immune response and caused an inhibition of MOG-specific antibody production (20,21). The expression of DB11 to MHC/HLA Class II protein, DR15, and the chemokine receptor CCR5 was also down regulated in both monocytes and macrophages. In all these studies, AFP served to decrease virous aspects of neuroinflammation, including disease severity, axonal loss and damage, T-cell reactivity, and antigen presentation (19,20). In subsequent experiments by other investigators, the immunomodulation of EAE by AFP was associated with elevation of immune cell apoptosis and increased levels of transcription factor FOXp3 (11). AFP was further found to increase the expression of the pro-apoptotic factors BaX, Bid, and others in peripheral lymphocytes. This increase was accompanied by an increased expression of transcription factor FOX p3 in lymph node cells as well as accumulation of DC4+ FOX p3 + regulatory T-cells in the CNS (19,20).

IV. Multiple Sclerosis and Pregnancy: Influencing Factors:

It is well-accepted that the pathogenic mechanisms in autoimmune disease (AD) pregnancies are a consequence of cellular immune processes and that the pregnant state invokes the emergence of systemic immunosuppressive factors in the mother during remission (21). Such local non-specific soluble factors produced by the mother, fetus, and/or placenta are thought to play a major role in retaining the fetus as an allograft (foreign body) within the mother (20). The soluble factors possess immunomodulatory properties and are produced in excess at the fetoplacental interface in order to prevent fetal-host allograph rejection (8). Such candidate factors have been identified as AFP; pregnancy-specific B1 glycoprotein, cytokines (IL-6, IL-10, INF alpha), tumor necrosis factor-alpha (TNF-alpha), prostaglandins, kinases, ion channels, and sex steroid hormones such as hydroxyl-estrones (23,24,25) (See below).

At least seventy percent of MS pregnant women are known to experience relapses within the first seven weeks following delivery. The number of CD8 suppressor T-cells have been decreased, and the CD4 helper cell-to-CD8 suppressor T-cell ratios are known to increase in pregnancy MS patients compared to normal pregnant women (26,27). Overall, there was no evident relationship between the T-cell number ratios and clinical disease activity even though differences were found in suppressor T-cell numbers. Also a reduction in the peripheral population of CD4 helper - cells have been reported during MS pregnancy with consequent lowering of the helper-to-suppressor T cell ratios (28,29). It is of interest that increased helper-to-suppressor T-cell ratios have been reported and associated with MS increased activity in non-pregnant MS patients (30). Moreover, AFP levels in these MS pregnant patients were not elevated, but rather decreased.

B) Alpha-fetoprotein and immunomodulation

Alpha-fetoprotein (AFP) is an immunomodulatory factor known to either enhance or inhibit the immune response (20,21). Recombinant human AFP has been reported to reduce autoimmune-induced visceral and neuroinflammation and to increase apoptosis to activated immune cells by reducing access to BCL-2-related pathways; in addition, AFP was also found to increase the expression of apoptosis FAS-related (CD95) cell death ligands (9,11). Furthermore, AFP increased both FOX p3 transcription factor expression in lymph nodes and T-reg cell number in several autoimmune disorders (12). AFP has been studied in animal models of MS (EAE) and found effective in treating and preventing its induction and progression (12-14). AFP at physiological levels exerts significant immunosuppressive effects on T-cells *in vitro* and has the ability to induce suppressor T-cells in autoimmune diseases (31,32). Overall, many investigators have now reported a beneficial effect of AFP on the course of MS in rat models and in human patients (33,34). Pregnancy fluids enriched with AFP have been shown to inhibit *in vitro* interactions of antibodies to autoimmune antigen (BMP) receptors binding to the myelin sheath (33).

The immune system in normal pregnancy does not produce immunosuppressive states but rather an immunotolerant state with the mother adapting to the fetus as a uterine allograft (21). For MS patients during pregnancy, four biological changes have been reported to occur (34.) First, levels of a number of hormones increase markedly and then drastically decrease following birth; these include estrogens (especially estriol), progesterone, prolactin, and glucocorticoids (35,36). These hormones induce shifts in cytokine levels, decreases in the presence of adhesion molecules and metalloproteinases, decreases in antigen presentation to dendritic cells, and boosts in the numbers of regulatory T-cells (T-regs). Such effects result in an overall decrease in inflammatory responses in the body of AD patients (37,38). Secondly, significant immune cell numbers are altered during MS pregnancy which involve T-regs, T-helper cells, and natural killer cells. Thirdly, fetal-derived antigens are released which interact and stimulate maternal immune T-reg and dendritic cells (antigen-presenting cells) in flare ups (relapses) (39). Interestingly, some MS pregnancies may result in positive beneficial effects to the maternal CNS by promoting recovery repair mechanisms and enhancing the ability to respond to immune mediated injury (see demyelination below). Overall, reports of patients with MS have shown marked improvements in neurological symptoms during the course of pregnancy (33)

C) The De-myelination Process:

The de-myelinization process during MS can be ascribed to activated T-helper cells binding to basic myelin antigens (BMPs) presented in conjunction with immune-activated MHC class-II molecules. Activated T-cells within the CNS release cytokines which promote an inflammatory response leading to enhanced activity of CNS microglial and killer T cells (40,41). Three major pathways of immune responses are involved in MS; 1) the pro-inflammatory Th-1 and Th-17 lymphocyte pathways which promote disease development; 2) the Th-2 cells which exert a protolerant effect against MS disease; this results in pro-inflammatory cascades which attack the nerve cell myelin sheaths; and 3) detection of infectious agents which are thought to prime the T-cells to penetrate the CNS. This produces an inflammatory response that initiates an ever progressive de-myelinating process on the nerve cell membrane surface (42,43).

D) Multiple Sclerosis disease Impact on Pregnancy:

The impact of pregnancy on MS is only slight and no adverse effects have been reported (33). Furthermore, MS patients are informed that their disease has no meaningful impact on the ability to conceive, on pregnancy itself, the ability to give birth, or the status and well-being of the fetus (44,45). Furthermore, no notable increases in spontaneous abortions, ectopic pregnancies, cesarean deliveries, or major obstetric complications have been demonstrated. Furthermore, pregnancy had no impact on the long term progressive course of MS or the likelihood of a secondary advanced progression of MS (46). Moreover, pregnancy and childbirth in MS have not been associated with further long-term disabilities and MS had no effect on fertility and family planning. However, there are precautionary factors associated with MS during pregnancy which include: Vitamin D deficiency, late maternal initiation of prenatal care, maternal overweight/obesity, diabetic pregnancy, maternal immune related medical conditions, cigarette smoking, addiction, excessive alcohol, and heavy caffeine use. Risks from a previous pregnancy may exist only if fetal loss, placental complications, and preterm delivery had been experienced (47,48). Many patients have gone through cycles of MS remissions and relapses prior to, during pregnancy, and in the perinatal/ puerperium period. Previous reports from the biomedical literature demonstrated that the AFP biomarker often predicted late term distress and other pregnancy complications which included preterm birth, low birth weight, pre-eclampsia and anormal placental events (12, 13). In prior pregnancies, most of the MS case studies of MS patients had reported delivery of normal term infants free of anatomical defects. After being counseled on the effects of certain medications (prednisone, corticosteroids) which the MS patients had taken prior to and during early pregnancy, most women agreed to continued gestation and undergo additional testing which included MS-related assays which included serum autoantibody determinations (49,50).

V

The immune system during pregnancy develops a state of immunocompetence *in utero* and an immunotolerant state in the mother whose body is adapting to a natural-occurring uterine foreign allograft. For MS patients in pregnancy, several immunobiological changes are seen to occur (20,21). First, a number of hormone levels increase markedly and then fall drastically following birth; these include estrogens (especially estriol), progesterone, and prolactin. In comparison, AFP normally decreases at birth and in the postpartum period. Such factors serve to cause shifts in cytokine levels, decreases in the number of adhesion molecules, modulation of antigen presentation to dendritic cells, and immunoregulation of the numbers of T-cells subset populations; some of which result in decreased immune responses (51,52). Second, significant enhancement of both humoral and cell-mediated immune responses have been reported to occur. Third, additional immunoprotective soluble (hormones, growth factors) proteins are produced which coincide with remission in the second and third trimesters. Fourth, autoimmune disease detrimental effects have not been observed to occur in the fetus. However, a few neonates have been known to experience a transitory MS, some of which display various low-grade symptoms of ADs (53,54)

VI. Additional Computer Supporting Data: A Search for Pairing of Peptide-to-Protein Interactions:

AFP and its derived peptides are bristling with matching amino acid segment sites from cytokines, chemokines, and immune system amino acid sequence identities which occur all over the AFP polypeptide molecule (45). The protein-to-protein and peptide-to-protein pairing computer software from serometrix revealed that the GIP peptide contained multiple matched allosteric amino acid pairing interaction sites with cellular immune-associated protein molecules; such proteins are the hallmark of diseases specific to MS. This software focused on the amino acid pairing of small amino acid fragments present on immune associated cells associated with MS disease. Such protein sites (amino acid segments) are potential targets for therapeutic changes (46,47). Such pairing interactions could affect signal transduction pathways by inhibiting (or enhancing) receptor binding by blocking peptide-to-protein interactions. As shown in Table-1, the matched interacting sites with GIP included: A) nerve cell (neuron) toxic proteins; B) chemokine/receptor proteins; and C) cytokine (immune associated hormone proteins), and ion channel proteins. These targeted pinpointed interactions with proteins of the cellular immune response system might cause the autoimmune disorder to progress to the severe symptoms which are observed clinically in MS disease patients.

Accession Number	Name of AFP Interacting Protein	Function of Interacting Protein
1. NP_000596	Interferon, alpha 2	First cytokine identified; anti-proliferative factor, innate immune response
2. NP_076435	Ly-6 neurotoxin-like protein 1 isoform a	Enables acetylcholine inhibitor activity and ion channel inhibition activity
3. O14626	G-protein coupled receptor 171 (H963)	G-protein-coupled nucleotide receptor activity in regulation of myeloid cell differentiation
4. O60674	Tyrosine-protein kinase Jak2	A member of Janus Kinase family of non-receptor protein kinases; a cytoplasmic signaling component of cytokines proteins
5. P43403	Tyrosine-protein kinase ZAP-70	A kinase in T-cell immune signaling responses by antigen receptors; a cytoplasmic tyrosine kinase phosphoprotein in T-cell development & activation
6. Q08881	Tyrosine-protein kinase ITK/TSK	Interleukin-2-inducible T-cell kinase in T-cell proliferation and differentiation in TH2 and Th17 cells
7. P60568	Interleukin-2 precursor (IL-2)(T-cell growth factor)	IL-2 is a potent mitogen and growth factor, it drives cell cycle progression and expansion of CD8 immune T-cells
8. Q02556	Interferon regulatory factor 8 (IRF-8)	Regulates expression of ceramidase and infection in disease states; possess DNA-binding domains
9. Q9Y2R2	Tyrosine-protein phosphatase non-receptor type 22	Relays signals form outside the cell to nucleus that instructs cells to grow, divide, and mature to special functions of T-cells
10. NP_000408	Interleukin 2 receptor, alpha chain precursor	A T-cell growth factor for T-lymphocytes of both CD4 and CD8 T-cells to secrete cytokines

11.Q07011	Tumor necrosis factor receptor superfamily member 9 precursor (CDw137)	A cytokine that regulates immune system of monocytes, macrophages, T-cells, B-cells and dendrites
12. O75293	Growth arrest and DNA damage-inducible protein GADD45 beta	Targets p21 in growth cell cycle, reduces nuclear cyclin B1 protein & inhibits CD kinase
13. NP05728	Forkhead-BOXP3 (FOX P3 Gene)	Master gene CD4+ T-cell regulatory (Treg) function. A transcription factor for production and function of immune regulatory T-cells
Part II: Potassium and Other Channels		
1.P51787	K-Channel M2	A muscarinic potassium (K) channel in the heart causing outward current of K, slowing the heart rate
2. NP00223	K-Channel Kv1.3	Channel present in vascular smooth muscle for cell migration, reflects detection of metabolic state
3.NP004965	K-Channel Kv1.2	Channels in heart and brain, functional roles in neurons, regulation of synaptic membranes
4. AAH58266	TRP-M1; Transient receptor potential (M-1 family)	A cation channel of the metastin family; expressed in metanocytes associated with development of melanomas, permeable for Ca^{++} and Zn^{++} ions
5. NP060124	TRP-M6 transient receptor potential (M-6 family)	A channel permeable to Ca^{++} and Mg^{++} ions. Regulates parathyroid hormone production, energy production, and DNA maintenance

*Note: The computer software was developed and generously provided by the Serometrix LLC Biotech Co, Pittsford, New York,14534 (See published references, 46 & 47). Asscession numbers were derived from the Protein Data Bank (See Ref 57).

Table-1: Molecular docking and protein interaction sites on alpha-fetoprotein and Growth Inhibitory Peptide (GIP) were identified. Such sites were localized by means of proprietary computer software (Peptimer Discovery Platform). See legend below.* The amino acid segment of human alpha-fetoprotein and Growth Inhibitory Peptide (GIP) that were probed for computer interaction sites employing allosteric modulation designs. The single letter protein amino acid code was used for the Human alpha fetoprotein amino acid sequence 445-480 as follows:

NH2-L S E D K L L A C G E G A A D I I T G H L C I R H E M T P V N P G V N P G V G Q-COOH

VII. Summary and Conclusion:

From the case reports, clinical studies, and experimental reports in the present review, it can be ascertained that autoimmunity during pregnancy is not necessarily a debilitating disease (33). Although pregnancy loss and adverse outcomes may be slightly increased in autoimmune inflicted mothers, the vast majority of women are successful in childbearing. Moreover, women with autoimmune disease do not appear to be at a significant risk for other pregnancy problems such as: pre-term birth, preeclampsia, or fetal growth restriction. During pregnancy, MS activity manifests two major pregnancy periods of remission, that is, a period of profound reduction of autoimmune symptoms (remissions) in the third trimester followed by an exacerbation of disease (relapses) in the postpartum/puerperium stages before returning to the pre-pregnancy state. Present and past data support the accepted conclusion that autoimmune progression is not worsened but may actually be reduced during certain gestational weeks of pregnancy. Local non-specific immunosuppressive soluble factors, such as AFP produced by the mother, fetus, and placenta, are thought to play a major roles in retaining the fetus as an allograft within the mother. Such soluble factors might normally be produced in excess at the fetoplacental interface in order to prevent fetal allograft rejection of a foreign body by the mother.

It can be readily ascertained from the present report that AFP is a major immune-associated soluble factor in ADs during pregnancy and it in postpartum stages. The humoral and cellular immunomodulatory activities of AFP present in this report have included: T-cell suppression, down-regulation of dendritic antigen expression, reduced autoantibody production, impairment of macrophage and T-cell function, and enhanced expression of cytokines, chemokines, interleukins, and growth factors. This study could serve to aid and benefit basic researchers, physicians, clinicians, and practitioners for treatment of autoimmune disease in the biomedical community at large.

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Conflict of Interest:

The author declares that there are no known conflicts of interest in the preparation of this manuscript.

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