Absence of Mannose-Binding Lectin in a Female with Relapsing-Remitting Multiple Sclerosis

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KEY WORDS: mannose, mannan, multiple sclerosis, complement, autoimmunity

IMAJ 2012; 14: 333–334

Mannose-binding lectin (also known as mannan-binding lectin) is a component of the innate immune system which recognizes repetitive sugar groups on the surface of bacteria and viruses leading to activation of the complement system [1]. While deficiency of the MBL protein can be present in up to 10% of the general population, the majority of individuals with MBL deficiency are asymptomatic due to redundancies in the immune system [1]. However, clinical manifestations of MBL deficiency have been associated with conditions that result in immune suppression and, interestingly, MBL deficiency has recently been associated with autoimmune diseases including systemic lupus erythematosus and rheumatoid arthritis [2]. Its role in other autoimmune disease, if any, has not been well studied, and to the best of our knowledge there are no reports of MBL deficiency associated with multiple sclerosis. We report here on a young adult with relapsing-remitting multiple sclerosis in whom MBL levels were undetectable.

PATIENT DESCRIPTION

We present the case of a 27 year old woman with relapsing-remitting MS in whom MBL levels were undetectable. She was first diagnosed with MS 4 years earlier, after she manifested symptoms of ataxia, vertigo, urinary incontinence, and vision changes consistent with optic neuritis. Episodes of optic neuritis and visual changes responded well to systemic corticosteroids. She continued to suffer from progressive lower extremity weakness and unsteady gait associated with frequent falling. Magnetic resonance imaging of brain revealed new 3 mm left middle frontal gyrus enhancement foci compatible with active demyelination, but otherwise stable multifocal cerebral white matter and corpus callosum T2 hyper-intensities in 2009. The most recent (2010) brain scan showed minimal progressive non-specific white matter changes with a solitary enhancing lesion, and 4 mm inferior tonsillar ectopia with mild crowding at the foramen magnum. Magnetic resonance imaging of the cervical spine in 2009 demonstrated mild degenerative changes with mild kyphosis of the mid-cervical spine, smudgy signal changes with the spinal cord at C6-C7, with features consistent with a demyelinating process. In 2010, cervical spine scan showed minimal degenerative changes. Since the time of her diagnosis, she had attempted several treatment regimens including glatiramer acetate, interferon beta-1a, and interferon beta-1b, but discontinued each due to worsening depression and anxiety. Natalizumab, the humanized monoclonal antibody against the cellular adhesion molecule α4-integrin, was being considered as the next potential therapeutic approach. Her neurologist also recommended consultation with an allergologist/immunologist in view of her history of chronic sinus infections, allergic rhinitis, skin folliculitis, and recurrent urinary tract infections with an approximate frequency of six urinary tract infections per year.

The patient also reported depression, anxiety, migraines, and polycystic ovary syndrome. Her current medications included: ethinyl estradiol and norethindrone, duloxetine, buspirone, aripiprazole, alprazolam, dicyclomine, ranitidine, omeprazole, acetaminophen, butalbital, baclofen, darifenacinhydrobromide, meclizine, diazepam, and fexofenadine. Her most recent MS relapse occurred 1 month earlier, and she was treated with systemic corticorticosteroids. The patient is a current smoker at 10 cigarettes per day for approximately 7 years. She rarely consumes alcohol beverages. She is married, without children, and has two cats in her home. Her biological parents had hypercholesterolemia, and no history of autoimmune disease or recurrent infection.

During her allergy and immunology evaluation, physical examination was essentially unremarkable apart from the fact that the patient was noted to be obese with a body mass index of 46.8 and weight of 110 kg. Skin folliculitis on the chest was also noted. Laboratory testing revealed an MBL level of 0 ng/ml (reference range ≥ 50 ng/ml), which was subsequently confirmed 2 months later by an independent laboratory. Other pertinent laboratory testing revealed elevated levels of C3 (186 mg/dl, range 90–180 mg/dl), complement CH50 (209 CAE units, range 60–144 units), C-reactive protein (23.0 mg/L, range 0.0–5.0 mg/L), and C1Q binding (4.6 µgE/ml, range 0.0–3.9 µgE/ml, standard reference value for the Raji cell immune complex assay). C4

MBL = mannose-binding lectin
MS = multiple sclerosis

level was normal at 25 mg/dl (10–40 mg/dl). Quantitative immunoglobulins were essentially normal with a total IgG of 1082 mg/dl (676–1512 mg/dl), IgA 130 mg/dl (60–378 mg/dl) and IgM 232 mg/dl (46–211 mg/dl). Following vaccination, laboratory tests demonstrated adequate titer responses to diphtheria and tetanus toxoid (protein-conjugated vaccines) as well as Streptococcus pneumococcal vaccination (polysaccharide vaccine). Antinuclear antibody panel, celiac disease panel, antimitochondrial antibody, rheumatoid factor, human immunodeficiency virus, and thyroid function tests were normal. Allergy skin prick test demonstrated significant sensitization to house dust mite and cat dander.

COMMENT

This case is unique due to the complete absence of MBL protein within the context of a young adult with multiple sclerosis. MS is a chronic demyelinating disease of the central nervous system and is generally considered to be an inflammatory autoimmune reaction against CNS antigens, resulting in tissue damage and significant neurological disability [3]. The etiology of MS is not well defined, but it is believed that complex genetic and environmental components contribute to disease susceptibility [3]. Infectious agents such as human herpes viruses and human endogenous retroviruses have been implicated, but no causal bacterial or viral agent has been unequivocally demonstrated in MS [3]. In addition, the pathogenesis of MS encompasses multiple inflammatory and apoptotic processes. The adaptive immune system is well recognized as playing a major role in the pathogenesis of MS, but recently the role of innate immunity has gained significant attention [3]. The complement system is important in innate immunity, which functions in host defense against pathogens, clearance of immune complexes and apoptotic cells, and interfacing between innate and adaptive immunity [1]. In general, the complement system has been implicated in MS pathogenesis, in part, because of the presence of complement components in demyelinating plaques and in the serum and cerebrospinal fluid of MS patients [3]. There are three pathways through which complement can be activated: classical, alternative, and lectin. All pathways converge, resulting in the generation of opsonins and anaphylatoxins as well as the formation of the membrane-attack complex that lyses cells [2]. Thus, it is possible that dysfunction or dysregulation of the MBL pathway could play a role in the pathogenesis of MS.

Of the studies investigating the role of MBL deficiency and autoimmunity, particular focus has been on SLE [2]. Namely, several studies show significant association with MBL deficiencies and SLE (with a nearly twofold increase in susceptibility), even across several ethnic backgrounds [2]. Moreover, reduced levels of MBL have been associated with juvenile-onset SLE and an increased risk for cardiopulmonary complications and cutaneous manifestations [2]. To the best of our knowledge no study has shown a correlation between MBL deficiency and MS severity; however, there are reports demonstrating that higher levels of MBL in patients with MS are associated with low disease activity, suggesting a protective effect of MBL [4].

Despite the potential correlation between MBL deficiency and autoimmune diseases, its exact role is not well defined. However, it is believed that MBL may act as a disease modifier by priming or promoting inappropriate immune and inflammatory responses. Notably, MBL is known to facilitate the clearance of apoptotic cells by binding to and initiating their uptake by macrophages [5]. Loss of this function would lead to an accumulation of cellular debris that could serve as a source of autoantigens. Alternatively, loss of MBL may render the patient more susceptible to other pathogens, particularly viruses, which may have a role in autoimmune disease progression. In our case, the patient did demonstrate evidence for increased infection susceptibility marked by recurrent sinus infections, folliculitis, and urinary tract infections. Interestingly, she also demonstrated a potential compensatory response for the apparent lack of MBL by increased activation of the complement cascade (CH50), C3, and C1q binding proteins.

Considering the integral role of MBL in the innate immune system and its established association with certain autoimmune diseases, it may be beneficial to assay for MBL levels in patients with MS where the relationship may not be as well characterized. This may be particularly important for MS patients with recurrent infections or when determining potential therapies that may result in further immune suppression. Finally, further studies may also be warranted to determine the potential role of MBL and MS as there might be a possibility of providing replacement MBL in the future.

Ig = immunoglobulin
CNS = central nervous system
SLE = systemic lupus erythematosus

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