



An Interesting Case of Multiple Sclerosis Presenting As Fever

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) which usually begins in early adulthood and is characterized by tissue inflammation, demyelination and gliosis, various degrees of axonal pathology, and episodic or progressive neurological disability. More than 1.5 million people worldwide and at least 400,000 individuals in Europe alone are affected by MS, which is second only to trauma as a cause of acquired disability in young adults in most Caucasian populations¹

Genetic and environmental factors jointly determine the susceptibility to develop MS. Collaborative efforts during the past years achieved substantial progress in identifying genetic risk factors that predispose for MS²

The role of environmental as opposed to genetic risk factors in MS is much less well defined, despite the fact that infections have long been thought to critically contribute to disease development. observations led to the development of the field of human genetics of infectious diseases and the identification of genetic traits that predispose to infection and clinical disease development³The insight that clinical infectious diseases result from complex interactions between the infectious agent, the environment, and host

factors rather than following a simple ‘one organism–one disease paradigm’ has implications for our understanding of how infectious pathogens might trigger complex autoimmune diseases such as MS. Current data suggest that infectious agents that contribute to MS development are most likely ubiquitous and highly prevalent in the general population. Moreover, they require a permissive genetic trait that determines the susceptibility of the host to develop MS. Finally, the distinct conditions, under which primary infection with these pathogens is encountered, might further modulate disease risk. Here, we review new data for an association of certain infectious pathogens with MS and illustrate mechanisms of infection-induced immunopathologies in experimental animal models of autoimmune CNS inflammation.

Case Report

38 Year old male came with chief complaints of Fever with chills since 5 days

Weakness in both lower limbs since 3 days,

Urinary retention since 2 days

Constipation since 2 days

Patients was apparently alright 5 days back when he developed fever sudden in onset high grade, associated with head ache.

Weakness in both lower limbs gradually progressing such that patient was unable to walk without support and ultimately wheel chair bound. Urinary retention such that patient earlier had urgency increased urinary frequency and then patient was unable to pass urine since 2 days Constipation since 2 days , patient also gives history of similar episode 2 years back when he had blurring of vision with double vision during fever which was sudden in onset which was not investigated and recovered after 10 days after subsidence of fever.

No history of, back ache

Trauma

Tuberculosis

Weakness in upper limbs

On examination

Pulse – 93/min Blood Pressure – 126/82mmhg

Respiratory Rate- 19/min

Temperature – 99.5 F

Central Nervous System –

Conscious oriented in place time and person

Higher mental function – normal

Motor System

Power u/l– 5/5

l/l– 1/5

Tone – u/l – normal

l/l- spastic

Sensory – u/l – normal

l/l – absent

Deep tendon reflexes u/l – normal

l/l – brisk

Plantars – extensors

Cerebellar signs – u/l normal

l/l- could not be elicited

Respiratory System- Within normal limits

Cardiovascular System – Within normal limits

Gastro Intestinal System-. Within normal limits

Investigations

HB -11.2GM/DL Platelets -320000 lakh /

cmm WBCS-4500/cmm

CSF Examination -Proteins- 55mg/dl

Wbcs-5 , lymphocyte – 90%

ANA Blot – Negative

HIV 1 AND 2 –

Negative

MRI Report- Multiple periventricular lesions that enhanced after gadolinium scan.

Diagnosis- Relapsing Remitting Type Multiple Sclerosis.

Treatment

Patient was given IV Methyl prednisolone 500mg 12 hourly for 5 days and then shifted to oral Methyl prednisolone 40 mg twice a day and the doses were tapered.

Patient was explained about interferon beta therapy but the patient refused due to high costs of the drugs. Hence patient started on Tab azathioprine 50 mg twice a day.

Tab baclofen 5 mg twice a day

Patient was treated along with supportive therapy with stool softeners, Foleys catheterisation was done for retention of urine,

Patient was counselled about healthy lifestyle habits and exercises.

Patient counselled about the future attacks.

Currently patient is stable, has been advised to follow up with hemogram and liver functions test monthly.

Discussion

Several mechanisms have been proposed to explain how pathogens such as viruses might trigger autoreactive immune responses in MS. These include virus-induced general activation of the immune system and the provision of viral gene products that specifically stimulate immune responses which cross-react with self-antigen

Mechanisms of bystander activation

Infectious agents express specific pathogen-associated molecular patterns (PAMPs). These are recognized by immune cell receptors leading to cellular activation, which increases the antigen-presenting capacity and the expression of costimulatory molecules by antigen-presenting cells (APCs), as well as their production of type I interferons, pro-inflammatory cytokines and chemokines, which in turn initiate and direct the

immune response against the invading pathogen. Thus, pathogens are recognized as adjuvants for the immune response against them and could, via pattern recognition receptor (PRR)-mediated activation of APCs that contain self-antigens obtained from dying cells or tissue damage, activate autoreactive T and B cells. Alternatively, the Th₁-driven environment during viral infection could facilitate activation of autoreactive bystander T and B cells via proinflammatory cytokine production. An even broader form of bystander activation is achieved by microbial superantigens, which cross-link MHC class II molecules with TCRs that contain a certain V β domain, leading to T-cell activation independently of specific antigen recognition. Staphylococcal, mycoplasma, endogenous retrovirus-derived, and enteric microbiota-generated superantigens were suggested to be involved in the disease exacerbation in animal models of MS^{4,5,6}

Conclusions

Although many epidemiological studies link VZV to MS, a report evaluating 40 studies in the period 1965–1999 indicated that there is insufficient evidence to support the association of MS with varicella or zoster infections. Two virus variants have been identified, HHV-6B, associated with mesial temporal lobe epilepsy (MTLE), and HHV-6A, which has primarily been associated with MS. DNA from HHV-6A was detected in brain tissue, serum, and CSF of some MS patients^{5, 6,7,8}. Exacerbation of relapsing-remitting MS has been linked to higher viral loads in serum^{9,10} and in peripheral blood mononuclear cells (PBMCs)¹¹, suggesting association of HHV-6 reactivation with disease relapses. Evidence for a potential role of EBV in the development of MS arises from reports on the positive correlation between clinical history of IM and MS occurrence^{12,13}, . The risk of MS has been suggested to increase after IM and to persist for at least 30 years after infection¹⁴. A recent meta-analysis reviewed 14 studies, 11 case-control and 3 cohort studies, which investigated the association of IM and MS. The

analysis concluded that the combined relative risk for development of MS after IM was 2.3 and in HLA-DR2-positive individuals even 7¹⁵, indicating that symptomatic EBV infection is a risk factor for MS¹⁶. A founding member of the HERV-W family, known as MS-associated retroviral agent (MSRV), is presumably a complete replication-incompetent virus capable of forming extracellular infectious virions^{17,18}. MSRV has been repeatedly isolated from CSF and blood of MS patients^{19,20}, as well as from body fluids of individuals with other neuroinflammatory disorders, but is less frequently observed in healthy controls²¹. The relationship between infections and autoimmune diseases is complex and the mechanisms by which infectious pathogens could trigger MS are likely dynamic, i.e., they might change over time and not be mutually exclusive. Epidemiological observations indicate that viral infections could contribute to MS development not only as triggers of disease exacerbations but also as etiological agents, i.e., long before the disease becomes clinically apparent. Although one particular MS-causing agent might still be discovered, current data suggest that multiple infections along with noninfectious environmental factors trigger the development of MS. These factors are likely ubiquitous, i.e., highly prevalent in the general population, and they require a permissive genetic background that predisposes for MS development. Future studies investigating infectious pathogens in a complex and heterogenous disease such as MS will benefit from careful and detailed clinical, pathological, and neuroimaging-based patient characterizations and from reproducibility in different study populations. In addition, novel humanized animal models of autoimmune diseases that are simultaneously permissive for viral pathogens which usually infect only humans^{22,23} should allow investigation of specific aspects of host-pathogen interactions during autoimmune CNS inflammation *in vivo*. The integration of these data might eventually allow us to better define the role of viruses in the etiology

and pathogenesis of MS and how virus–host interactions could be targeted for MS therapy^{24,25,26,27}.

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