One Pathogen but Three Immune Responses with Three Neurologic Outcomes

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Measles is a highly contagious illness caused by paramyxovirus family virus. Almost all non-immune children contract this respiratory disease if exposed to the virus. While immunization effectively controls the incidence of measles, decreasing rates of immunization in developed regions and lack of access to immunization are allowing the immunologic side effects of measles to emerge as a significant health risk. Here we present three rare complications of measles infection to demonstrate the consequences of too much, too little or just the wrong type of neuroimmune responses.

1. An immune response sufficiently effective to clear a pathogen can also cause lethal brain damage after the pathogen has been effectively cleared. For example, acute post-infectious measles encephalomyelitis (APME) is characterized by abrupt onset of fever, seizures and multifocal neurological signs one to two weeks after appearance of the measles rash and is fatal in 10–20% of patients. Despite the absence of detectable measles virus in the CNS of these patients, clinical features of APME correlate with robust influx of blood-derived macrophages and lymphocytes into the CNS. The sum of the published data suggest that during immune-mediated clearance of measles from the body, pathogen-provided alarm signals (PAMPs) led to the inappropriate activation of T-cells able to recognize self-antigens in 0.1% of patients infected with measles.

2. Ineffective immune responses are ineffective in removing PAMP signals and thus promote chronic neurotoxic inflammation. Subacute sclerosing panencephalitis (SSPE) is a very rare complication of measles infection and is associated with continual low-grade inflammation of the CNS. Clinical symptoms emerge 5–10 years after systemic clearance of the measles virus

and include mental deterioration, appearance of myoclonus, optic atrophy and akinetic mutism. Based on experimental models, SSPE is presumed to result from CNS infection by partially defective measles virus particles incapable of budding from the surface of infected cells. The budding-defective viral clones are able to persist and spread throughout the CNS because of ineffective antigen presentation and detection of viral particles. Clinical pathology is likely the combined result of persistent production of TNF and IL-1β, accumulation of intrathecal oligoclonal IgG, as well as the persistence of measles virus within cells of the CNS.

3. Too little immunity can result in normally benign viruses, bacteria and parasites lethally disrupting brain function. In this situation, brain damage and/or death can be due to competition for metabolic components, to disruption of CNS intracellular signaling by pathogen products or to direct pathogen killing of CNS cells. Measles-infected children with viral or drug-induced immunodeficiencies cannot always control the viral infection, resulting in a general progressive neurological deterioration that includes seizures. Neuronal damage, astrogliosis and inclusion bodies in both neurons and glia are observed in brain pathology samples from infected individuals. The only effective treatment in this situation is to attempt to halt viral replication with antiviral drug therapies.

Sickness behavior is usually transient, disappearing with immune-mediated clearance of pathogen and the subsequent resolution of systemic immune responses (Dilger & Johnson, 2008). However, recent studies suggest that sickness behavior may facilitate the onset or relapse of clinical depression. It is speculated that susceptibility may result from hyperproduction of TNF, IL1 or IL6, hypoproduction of IL-10, or less-efficient serotonergic function as occurs with homozygosity for the short allele of the 5-HT transporter gene.