THE YALE JOURNAL OF BIOLOGY AND MEDICINE 53 (1980), 101-107

Types of Immunological Failure in the "Slow Virus" Encephalopathies and Multiple Sclerosis

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Received July 12, 1979

The pathogenesis of the slow virus encephalopathies and multiple sclerosis is reviewed within the framework of the immune response. The diseases are analyzed for the component of the immune response that appears to be crucial to the host's failure to control the disease. Thus, the absence of an immune response in the spongiform encephalopathies appears to reflect a failure of antigen recognition. Progressive multifocal leukoencephalopathy (PML), subacute sclerosing panencephalitis (SSPE), and progressive rubella panencephalitis (PRP) may result principally from a failure of effector mechanisms. In PML the failure usually occurs within the setting of an immunosuppressive illness. Conversely, in SSPE and PRP the effector failure seems to result from the nature of the host-virus interaction itself. Finally, evidence is accumulating that a defect of immunoregulation plays a significant role in multiple sclerosis.

INTRODUCTION

Despite remarkable progress, we are ignorant of much of the pathogenesis of the "slow virus" encephalopathies and M.S. For example, in progressive multifocal leukoencephalopathy (PML) it is thought that a papova virus attack on oligodendroglia is responsible for the impairment of myelin production. It is not known, however, what specific effector mechanism is required to prevent viral replication in the brain. Subacute sclerosing panencephalitis (SSPE) is associated with an abortive measles virus infection of the brain and a marked antibody response. What is not known are the features of the host-virus interaction which render the host defense response ineffective. In Creutzfeld-Jakob Disease (CJD) there is no evidence that the host recognizes any antigenicity in the transmissible agent. Finally, M.S. is thought by many to be a virus-induced, immune-mediated disease. Exacerbation and remission may result from fluctuation of immune regulation. However, this is not proven, nor have the reasons for the fluctuation been established.

It therefore seems appropriate to review these diseases in the context of the host immune response. The immune response will be considered as consisting of antigen recognition, effector mechanisms, and immunoregulation. In Table 1 the diseases are listed under the component of the immune response which appears crucial to the failure of the host to control the disease. This does not mean that the other components are necessarily intact.

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TABLE 1
Types of Immunological Failure in the
"Slow Virus" Encephalopathies and Multiple Sclerosis

1. Failure of Antigen Recognition
   Kuru
   Creutzfeld-Jakob Disease
2. Failure of Effector Mechanisms
   A. Generalized Immune Impairment
      Progressive Multifocal Leukoencephalopathy
   B. Specific Interactions of Host and Virus
      Subacute Sclerosing Panencephalitis
      Progressive Rubella Panencephalitis
3. Failure of Immunoregulation
   Multiple Sclerosis

FAILURE OF ANTIGEN RECOGNITION: KURU AND CJD

Experimental transmissibility of a fatal subacute encephalopathy with characteristic neuropathological changes are common features of the spongiform encephalopathies. These are scrapie and transmissible mink encephalopathy of animals and Kuru and CJD of humans [1]. Kuru, found exclusively in New Guinea, was transmitted to subhuman primates by Gajdusek and his colleagues. It has declined markedly since the termination of ritual cannibalism. CJD, in contrast, is found in many parts of the world. Its central clinical effect is dementia with myoclonic jerks and an electroencephalographic pattern of burst suppression. The neuropathological changes consist of the spongiform change, loss of neurons, and proliferation of glia [2].

Although extremely high infectivity titers in infected brain can be measured by transmission to experimental animals, conventional virus has not been isolated. Furthermore, these agents are unusually resistant to many treatments that destroy infectivity of conventional agents such as nucleases, proteases, heat (80°C), UV irradiation, and formaldehyde. They do, however, appear to be vulnerable to treatments which disrupt membranes [1], suggesting that they may be closely associated with host membranes. The insensitivity to conventional inactivation techniques coupled with accidental surgical transmission in humans has led to the formulation of safety procedures for handling CJD patients [3].

One of the most remarkable features of all the spongiform encephalopathies is the absence of any evidence of a host defense response. The brain contains no features of inflammation such as mononuclear perivascular infiltration, glial nodules, or phagocytic cells. Although the CSF protein may be mildly elevated, there is no CSF pleocytosis [4]. No evidence of serum neutralizing activity has been found, nor is there evidence of deposition of immune complexes. Furthermore, attempts to induce *in vitro* blastogenesis of leukocytes of diseased animals with infected material have failed [5]. Finally, it has not been possible to immunize against CNS disease in experimental scrapie infection of goats [6]. Thus, there is no evidence that antigen recognition occurs on exposure to this class of agent. Since disease does not occur in the setting of an immunocompromised host, it seems most likely that the failure of recognition relates to the agent itself. Demonstration or experimental induction of antigen recognition would be a significant contribution to the understanding of these diseases.

FAILURE OF EFFECTOR RESPONSE

Generalized Immune Impairment: PML

PML is a rare demyelinating disease of the central nervous system often occurring in the setting of an immunosuppressive systemic illness [7]. The neuropathology is characterized by foci of demyelination, bizarre apparently transformed astroglia, and destruction of oligodendroglia involving enlargement, intranuclear inclusions, and lysis. Papova virus originally identified by electronmicroscopy (E.M.) [8] has been isolated from PML diseased brains [9]. It is felt that the diverse clinical symptomatology results from impairment of myelin production in papova virus-infected oligodendroglia.

All but two isolates of papova virus from PML material have been the JC virus (JCV) type, the other two being SV40 [10]. JCV, a papova virus, is antigenically distinct from SV40 and from the human wart virus. It can be grown in primary cultures of fetal glial cells in which evidence of both cell lysis and cellular enlargement are found [10]. Recently it has been reported to replicate in human amnion cells [11]. It has been demonstrated that JCV is oncogenic *in vivo* [10]. The virus contains a hemagglutinin which has led to the development of an hemagglutination-inhibition test for antibody. Utilizing this assay, Padgett and Walker found that 69 percent of adults sampled in Wisconsin had antibody to JCV [12].

Often occurring in the setting of an illness which depresses the host defense capability, PML may involve a number of nonspecific humoral and cell-mediated immunity (CMI) defects. For example, Narayan et al. described immunological testing in five reported patients with PML [13]. The defects ranged from an isolated failure of lymphocytes to respond *in vitro* to phytohemagglutinin to combined defects of humoral and cell-mediated immunity. With regard to viral specific responses there has been documentation of humoral antibody to JCV in patients with PML [10,14]. Assays of CMI toward JCV are just beginning to be examined. Willoughby et al. have recently reported on six patients with PML who had detectable antibody to JCV [14]. No leukocyte inhibition factor was induced on exposure to JCV antigen when leukocytes from these patients were used, but it was induced from controls previously exposed to the virus. If this data is confirmed it would appear that antigen recognition occurred but that CMI was deficient. A critical question will then be to determine the nature of the protective effector mechanism.

Specific Interactions of Host and Virus: SSPE and PRP

SSPE, a disease of childhood, has a median age of onset of about nine years [15]. It follows an average of seven years after an apparently uncomplicated case of measles. The initial measles infection frequently occurs by two years of age [16]. The course of SSPE is from less than a year to a few years. It is fatal in at least 95 percent of cases with survival occasionally reported [17]. The course has been characterized as going through four stages beginning with behavioral abnormalities [18]. This is followed by the development of myoclonic jerks and spasticity, which evolves into marked spasticity and coma, with a final evolution to a reduction of myoclonus and spasticity prior to death. Males are attacked more frequently than females, and in the United States the highest attack rates are in the Southeast and upper Ohio River Valley [15].

Cases of SSPE, described as other entities, can be found in the literature of neuropathology as early as 1922 (reviewed in [19]). The principal neuropathological

features are widespread distribution of perivascular mononuclear infiltrates, fibrillary gliosis, demyelination, and Cowdry type A intranuclear inclusion bodies. The description of myxovirus nucleocapsid material in brain material by Bouteille et al. (cited in [19]) on E.M. initiated a series of observations associating abortive measles virus infection with SSPE. Later, Connolly et al. documented unusually high anti-measles antibody levels in serum and CSF [20]. Finally, Horta-Barbosa et al. reported the successful isolation of extracellular measles virus by cocultivation of passaged brain cells with a susceptible cell line [21].

A critical question concerning SSPE isolates is whether they differ consistently from measles virus. Hall and ter Muelen have reported that the genome of SSPE isolates contains 10 percent more information than measles virus genome [22]. Furthermore, Hall et al. have shown that the mRNA coding for the matrix (M) polypeptide has a higher molecular weight in SSPE virus than in measles virus and that the respective M proteins are antigenically distinct [23]. Concurrently, Wechsler and Fields reported that the M polypeptide of five SSPE isolates migrated differently than that of the Edmonston strain of measles virus [24]. Hall et al. did not find an electrophoretic pattern characteristic of SSPE virus [25]. They did find a relative lack of antibodies to the M protein in sera from SSPE patients. The role of the M polypeptide is presumed to be in nucleocapsid and cell membrane recognition during virus maturation. The effect of the altered M polypeptide in SSPE is not known. One possibility is that it might produce a measles-infected cell which is not susceptible to cytotoxic effector mechanisms of the host.

One of the major problems in understanding the pathogenesis of SSPE is the repeated demonstration of antiviral effector function in patients. Specific humoral immune function is demonstrated by high levels of circulating and locally produced antibody [18]. The presence of cell-mediated cytotoxicity against measles-infected targets has been demonstrated *in vitro* [26,27,28]. How then does the virus survive in the face of specific effector capability? At present there are at least three mechanisms resulting from virus host cell interaction to explain the failure of host effector mechanisms. First, circulating and CSF factors that block immune responses, possibly immune complexes, have been described [29]. Second, the proposal has been made by Oldstone and his colleagues that antibody strips viral antigen from infected cells, resulting in an antigenically modulated target no longer susceptible to cytotoxicity. That group has recently shown that surface antibody can also alter the production of viral protein within the cell [30]. Finally, an altered M polypeptide might result in a measles-infected cell no longer recognized by host cytotoxic effector mechanisms. The relative lack of antibodies to the M polypeptide in SSPE supports this concept [25].

The remarkable clinical pattern of SSPE, initial infection and resolution followed years later by a relentlessly progressive panencephalitis, also occurs in progressive rubella panencephalitis (PRP). Although incompletely characterized because of the paucity of reported cases, PRP has not been associated with a generalized defect of humoral or cell-mediated immunity [31]. The onset at the start of the second decade follows congenital or childhood rubella and progresses relentlessly over a few years with dementia and ataxia as principal features. Cerebellar atrophy, white matter destruction, perivascular infiltration, neuronal loss, gliosis, and amorphous vascular deposits characterize the neuropathology [32]. Rubella virus has been isolated from the brain and locally produced anti rubella antibody is found in the CSF [33]. The CSF IgG is elevated and oligoclonal bands containing anti rubella antibody are

found [34]. Thus, PRP is an illness in which viral antigens are recognized and a specific immune response produced. However, like SSPE, interaction of the virus and the host apparently allows the establishment of latency and, years later, the emergence of a destructive CNS disease.

FAILURE OF IMMUNOREGULATION:M.S.

Multiple sclerosis was established as a clinical-pathological entity over a century ago by J.M. Charcot. It strikes people between the ages of 10 and 50, impairs the function of multiple areas of white matter, and usually has a characteristic exacerbating and remitting course. Although it has long been suspected that M.S. has a viral etiology, no consistent proof for any single virus has emerged. However, the disease appears to be mediated by immune mechanisms. The neuropathology is essentially one of an inflammatory demyelinating process [35]. Active areas of demyelination, or plaques, have a rim of mononuclear cells, and the plaques can be shown to contain IgG [36,37]. Furthermore, a high association between M.S. and certain B lymphocyte alloantigens has been demonstrated [38,39]. Finally, the most consistent laboratory abnormality, but not diagnostic, is evidence of local CNS production of IgG as reflected in the cerebrospinal fluid. With the use of isoelectric focusing, the presence of oligoclonal bands of IgG has been found in the CSF of over 90 percent of patients with M.S. [40].

Although the immune specificity of the majority of the immunoglobulin in the CSF is undefined (reviewed in [41]), antibody to measles, vaccinia, and other viruses has been found in the CSF in the absence of a breakdown of the blood-brain barrier or the demonstration of an ongoing CNS infection. Thus, virus-specific antibody localized to the central nervous system is found in the apparent absence of the inducing agents. One explanation of this data would be the failure of the shutoff signal, immunosuppression, for antibody-forming cells in patients with M.S. Evidence for the non-specificity of the failure of immunosuppression is found in the work of Norrby et al. [42]. They found antibody in the CSF to measles in 57 percent, rubella in 19 percent, mumps in 15 percent, herpes in 11 percent, and sendai in 3 percent of 150 patients with M.S. Furthermore, antibody to two viruses was found in 16 percent and to three viruses was found in 7 percent. This indicates that more than one antibody-producing clone has failed to shut down and that the multiple antibody responses are not directed toward multiple antigenic determinants on a single complex agent. The most likely interpretation is a failure of polyclonal immunosuppression.

The concept that there is a failure of immunosuppression is supported by experimental studies of peripheral mononuclear cells *in vitro* for suppressor activity. Arnason and Antel have demonstrated a marked reduction *in vitro* of suppressor cell activity that could be induced by Concanavalin A during exacerbations of M.S. with a rebound of excess activity during recovery [43]. Our own pilot studies [44] and the studies of Neighbor and Bloom [45] support the finding of a failure of Concanavalin A induceable immunosuppression during exacerbations of M.S. The latter investigators found a reduced measles antigen induced suppressor activity irrespective of disease activity. Finally, Huddlestone and Oldstone found a transient decrease of circulating suppressor cells during disease exacerbation [46]. Clearly several crucial questions arise. If one could prevent impairment of suppressor cell function, could exacerbations be prevented? One would also like to know what causes the transient impairment of suppressor cell function.

CONCLUSION

Although the diseases have been discussed as reflecting types of failure of the host immune response, it is not anticipated that these defects will turn out to be isolated. Thus, it is entirely possible that defects of more than one type will be found in any given disease. It is hoped, however, that this analysis will generate experimental questions about the pathogenesis of the diseases.

ACKNOWLEDGEMENTS

I am grateful to Ms. Fran Bernstein and the staff of the Medical Library of the V.A. Medical Center for substantial assistance with the literature review. I am also grateful to Ms. Christine Covington for efficient manuscript preparation.

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