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A Theory of Virus-Induced Demyelination in the Landry-Guillain-Barré Syndrome

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Summary. The Landry-Guillain-Barré syndrome (LGBS) is a demyelinating disorder of the peripheral nervous system frequently preceded by infection with common viruses. Most prevalent among these agents are herpesviruses, particularly Epstein-Barr virus (EBV) and cytomegalovirus (CMV). The specific role played by antecedent viral infection in the pathogenesis of the LGBS remains obscure. In this regard, recent studies of Marek's disease (MD) neuropathy, an avian herpesvirus-induced experimental model for the LGBS, may provide insight. The autoimmune pattern of demyelination seen in MD neuropathy is histopathologically indistinguishable from that seen in the LGBS. In this paper, a comprehensive theory is discussed regarding the pathogenetic mechanisms that may be operative in the LGBS.

Key words: Landry-Guillain-Barré syndrome – Herpesviruses – Marek's disease virus – Epstein-Barr virus – Cytomegalovirus

Zusammenfassung. Das LGBS ist eine Myelin vernichtende Krankheit der peripherischen Nerven, der man häufig bei Infektionen mit allgemeinen Viren begegnet. Am häufigsten darunter sind Herpesviren, besonders das Epstein-Barr Virus (EBV) und Cytomegalovirus (CMV). Die spezifische Rolle einer vorhergehenden Virusinfektion in der Pathogenese von LGBS bleibt ungewiß. In dieser Beziehung mögen sich neue Studien über die Neuropathie von Mareks Krankheit (MD), eine von Vögeln getragene, durch Herpesvirus verursachte experimentelle Vorlage für die LGBS, als aufschlußreich beweisen. Die autoimmune Gestalt von Demyelination, die man in MD Neuropathie beobachtet, ist von der in der LGBS beobachteten Demyelinationsgestalt histopathologisch nicht zu unterscheiden. Diese Arbeit handelt von einer umfassenden Theorie bezüglich der pathogenetischen Mechanismen, die in der LGBS wohl operieren dürfen.

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The pathogenetic mechanisms underlying infectious demyelinating disorders of the peripheral and central nervous systems have been the subject of intensive study and speculation (reviewed by Lampert 1978). Viral infection, for example, may result in primary demyelination by a variety of mechanisms with and without a demonstrable immune component, as illustrated by subacute sclerosing panencephalitis and progressive multifocal leukoencephalopathy, respectively. In addition, viral infections may also trigger an autoimmune type of demyelination, characterized by the disintegration of myelin lamellae in the presence of perivenular mononuclear cell infiltrates. This specific allergic attack directed against the myelin sheaths rather than the myelin-supporting cells is a unique ultrastructural finding that has been described in virus-associated experimental systems i.e. in Marek's disease (MD) as described by Payne et al. (1976), Prineas and Wright (1972), and Lampert et al. (1977); in postinfectious Theiler's virus myelitis by Daniels et al. (1952), Lipton (1975), Dal Canto and Lipton (1975); and in the Landry-Guillain-Barré syndrome (LGBS) of man by Prineas (1972) and Wisniewski et al. (1969).

In this regard, the LGBS has recently received special attention as an autoimmune, demyelinating peripheral neuropathy which may present as a potentially serious complication of influenza vaccination (Halpin and Marks 1980). Although well over a century has passed since the first description of this disorder (Landry 1859), its etiology still remains undetermined. The reportedly high incidence of antecedent respiratory illness has implicated both viruses and *Mycoplasma pneumoniae* as likely etiologic agents (Leneman 1966). Recent studies (Dowling and Cook 1981) have revealed that cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections have been most commonly associated with the LGBS. In addition, the medical literature also contains several reports of the LGBS associated with varicella-zoster virus infection, although with lower frequency, as well as isolated, single case reports of antecedent infection with a variety of viral pathogens. Scattered reports of the LGBS accompanying gram-negative bacterial infection, vaccination, surgery, Hodgkin's disease, and immunosuppressive therapy (reviewed by Arnason 1975) have been particularly perplexing, since it is unclear whether these diverse antecedents share a common pathogenetic mechanism, operate through multiple and diverse etiologic pathways, or whether they are coincidental.

In an attempt to resolve these issues, studies of model systems for the LGBS may prove to be relevant. Marek's disease virus (MDV) is an avian herpesvirus which induces a lymphomatous and neuropathic disorder in chickens (Payne et al. 1976). The nerve lesions are characterized by scattered, lymphocytic infiltrates throughout the peripheral nervous system with focal areas of segmental and paranodal demyelination (Lampert et al. 1977). The peripheral neuropathy seen early in the course of MD is histopathologically indistinguishable from that seen in the LGBS of man (Borit and Altrocchi 1971) and is accompanied by similar clinical signs of paresis and paralysis. Several studies have demonstrated a cellular and humoral immune response to components of peripheral nerve and peripheral nerve myelin in the course of both MD neuropathy and the LBGS (reviewed by Arnason 1975; Payne et al. 1976). Finally, it is of particular interest, in view of the association of the LGBS and human herpesvirus infection (Dowling and Cook

(1981), that MD shares many immunological, antigenic and biological characteristics with EBV, and these agents may be regarded as pathogenetic counterparts in their respective hosts (Rapp 1974).

Recent studies of MD neuropathy (Pepose et al. 1981; Stevens et al. 1981) have revealed that the virus selectively establishes a latent infection in neuronal satellite cells and nonmyelinating Schwann cells in peripheral nerves and dorsal ganglia. During the latent infection, viral products cannot be detected in nervous tissue examined at necropsy by ultrastructural or immunohistochemical methods. However, explantation and in vitro cultivation of peripheral nerves and ganglia provide a stimulus which 'induces' the reactivation of the latent infection, with the appearance of viral antigens and capsids selectively in nonmyelinating Schwann cells. Neurons and myelinating Schwann cells, in contrast, do not appear to harbor the agent.

Given the striking immunobiological similarities between EBV and MDV (Rapp 1974) and the results of laboratory-based epidemiologic studies of LGBS implicating antecedent herpesvirus (i.e., EBV and CMV) infection (Dowling and Cook 1981), we propose the following theory of virus-induced demyelination in the LGBS. As was shown in studies of MD neuropathy (Pepose et al. 1981), primary infection with EBV may be similarly characterized by the virus establishing a latent infection in supporting cells in the peripheral nerves and ganglia, with the subsequent expression of a lymphocyte-detected membrane antigen. Virus-associated membrane antigens have been convincingly demonstrated on lymphocytes latently infected with both MDV (Ross 1977) and EBV (Svedmyr and Jondal 1975). Perhaps in the majority of cases, the expression of viral-induced antigen in a few, well-isolated Schwann cells and satellite cells elicits a limited immune response with some areas of focal, subclinical demyelination. The subsequent proliferation of T_5^+ suppressor lymphocytes, recently shown to be characteristic of EBV infection (Reinherz et al. 1980a), may serve to limit the immune response. However, in a few cases due to an aberrant and uncontrolled immune response and/or a more extensive latent infection, the release of proteases (Wisniewski and Bloom 1975; Norton et al. 1978) would result in more extensive lysis of myelin. The subsequent release of viral antigen may act as an adjuvant and enhance the processing of the myelin lamellae by macrophages, resulting in a vigorous immune response to myelin in a vicious cycle. In support of this theory, it should be noted that a recent analysis of peripheral blood lymphocytes in four LGBS patients revealed normal numbers of T_5^+ suppressor cells (Reinherz et al. 1980b). If these cases of the LGBS were the consequence of primary EBV infections, normally characterized by high levels of suppressor cells, then they may represent an aberrant immune response to EBV infection.

This theory may also account for the infrequent reports of the LGBS in association with various stressful events such as surgery, bacterial infection, and Hodgkin's disease (Arnason 1975). A literature review reveals that many of these LGBS patients were surprisingly young and could have recently contracted a primary EBV infection. These ancillary conditions (e.g., Hodgkin's disease, with lymphomatous involvement of nerve roots) may help to break the blood-nerve barrier and thereby allow the onset of the demyelinating immune response. Furthermore, conditions such as bacterial superinfection, therapeutic immuno-

suppression in graft recipients, or lymphoproliferative diseases may lead to an aberrant immune response to concurrent primary EBV infection. Finally, the possibility exists that these varied antecedent events may precipitate the LGBS via independent patterns of pathogenesis.

The means to test the basic tenets of this hypothesis currently exist. A prospective, multi-centered study of EBV infection and the LGBS would be in order, including extensive serologic studies and attempts at viral isolation from appropriate tissues. Although serologic studies may conclusively demonstrate primary EBV infection in many cases, the LGBS presenting as a late sequela of primary EBV infection may be associated with serologic evidence of long-standing EBV infection (Grose et al. 1975). In conjunction with this study, an analysis of circulating T-cell subsets should be carried out in patients shown to have a primary EBV infection associated with the LGBS, to determine whether they represent an abnormal immune response to the viral infection. In addition, since all cell lines harboring EBV have been shown to express a viral-induced nuclear antigen (Reedman and Klein 1973), nerve biopsies from LGBS patients can be tested for this antigen using appropriate immunologic methods. The advent of high affinity, monoclonal antibodies (Kohler and Milstein 1975) may enhance the sensitivity of this method. Finally, nervous tissue biopsy from cases of the LGBS should be maintained in organ culture and examined for viral reactivation in non-lymphoid cells with standard ultrastructural and immunohistochemical techniques.

References

Arnason BGW (1975) Inflammatory polyradiculopathies. In: Dyck PJ, Thomas RK, Lambert EH (eds) Peripheral neuropathy, vol II. SB Saunders, Philadelphia, pp 1110–1148

Borit A, Altrocchi PH (1971) Recurrent polyneuropathy and neurolymphomatosis. Arch Neurol 24:40–49

Dal Canto MC, Lipton HL (1975) Primary demyelination in Theiler's virus infection: an ultrastructural study. Lab Invest 33:626–637

Daniels JB, Pappenheimer AM, Richardson S (1952) Observations on encephalomyelitis of mice (DA strain). J Exp Med 96:517–530

Dowling PC, Cook SD (1981) Role of infection in Guillain-Barré syndrome: Laboratory confirmation of Herpesviruses in 41 cases. Ann Neurol (Suppl) 9:44–55

Grose C, Henle W, Henle G, Feorins PM (1975) Primary Epstein-Barr virus infections in acute neurologic disease. N Engl J Med 292:392–395

Halpin TJ, Marks JS (1980) Guillain-Barré syndrome in recipients of A/New Jersey Influenza Vaccine. JAMA 243:2490–2494

Kohler G, Milstein C (1975) Continuous cultures of fused cells secreting antibody of predefined specificity. Nature 256:495–497

Lampert P, Garrett R, Powell H (1977) Demyelination in allergic and Marek's disease virus-induced neuritis. Acta Neuropathol 40:103–110

Lampert PW (1978) Autoimmune and virus-induced demyelinating diseases. Am J Pathol 91:176–198

Landry O (1859) Note sur la paralysie ascendante aigue. Gashebd Med Chirurg 6:472–474

Leneman F (1966) The Guillain-Barré syndrome. Definition, etiology, and review of 1100 cases. Arch Int Med 118:139–144

Lipton HL (1975) Theiler's virus infection in mice. An unusual biphasic disease process leading to demyelination. Infect Immun 11:1147–1155

Norton WT, Cammer W, Bloom BR, Gordon S (1978) Neutral protein secreted by macrophages degrade basic protein: a possible mechanism of inflammatory demyelination. Adv Exp Med Biol 100:365–381

Payne LN, Frazier JA, Powell PC (1976) Pathogenesis of Marek's disease. Int Rev Exp Pathol 16:59–154

Pepose JS, Stevens JG, Cook ML, Lampert PW (1981) Marek's disease as an animal model for the Landry-Guillain-Barré syndrome. Latent infection restricted to neuronal supporting cells and accompanied by specific immune responses to peripheral nerve and myelin. Am J Pathol 103:309–320

Prineas JW (1972) Acute idiopathic polyneuritis. An electron microscope study. Lab Invest 26:133–147

Prineas JW, Wright RG (1972) The fine structure of peripheral nerve lesions in a virus-induced demyelinating disease in fowl (Marek's disease). Lab Invest 26:548–557

Rapp F (1974) Herpesviruses and cancer. Adv Cancer Res 19:265–302

Reedman BM, Klein G (1973) Cellular localization of an Epstein-Barr virus (EBV)—associated complement-fixing antigen in producer and non-producer lymphoblastoid cell lines. Int J Cancer 11:499–520

Reinherz EL, O'Brien C, Rosenthal P, Schlossman SF (1980a) Cellular basis for viral induced immunodeficiency: analysis with monoclonal antibodies. J Immunol 168:1233–1269

Reinherz EL, Weiner HL, Hauser SL, Cohen JA, Distaso JA, Schlossman SF (1980b) Loss of suppressor T cells in active multiple sclerosis: analysis with monoclonal antibodies. N Engl J Med 303:125–129

Ross LJN (1977) Anti-viral T-cell-mediated immunity in Marek's disease. Nature 268:644–646

Stevens JG, Pepose JS, Cook MC (1981) Marek's disease: A natural model for the Landry-Guillain-Barré syndrome. Ann Neurol (Suppl) 9:102–106

Svedmyr E, Jondal M (1975) Cytotoxic effector cells specific for B cell lines transformed by Epstein-Barr virus are present in patients with infectious mononucleosis. Proc Nat Acad Sci USA 72:1622–1626

Wisniewski H, Terry RD, Whitaker JN, Cook SD, Dowling PC (1969) Landry-Guillain-Barré syndrome: a primary demyelinating disease. Arch Neurol 21:269–276

Wisniewski HM, Bloom BR (1975) Primary demyelination as a non-specific consequence of a cell-mediated immune reaction. J Exp Med 141:346–359

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