Abnormal serum factors in Guillain-Barré syndrome

Lisak R.P., Brown M.J., Summer A.J.
Department of Neurology, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania U.S.A.

The Guillain-Barré Syndrome (GBS) is generally considered to be a cell-mediated immunopathologic disease of the peripheral nervous system (PNS), although the evidence for this is indirect. Both in vitro and in vivo studies of sera from experimental animals with autoimmune demyelinating neuropathies suggest that serum factors, including antibodies to PNS myelin and/or Schwann cells, may be important in the pathogenesis of some of these disorders. More recently, similar in vitro and in vivo techniques, including the production of demyelination following intraneural injection in the rat have been employed to study sera from patients with GBS. The results of these studies demonstrate the presence of factor(s), as yet not fully characterized, that may be important in mediating demyelination. Moreover, in some patients with chronic or relapsing demyelinative inflammatory neuropathies and monoclonal gammopathy, there is evidence of antimyelin antibodies to PNS myelin. Further studies of serum from patients with acute GBS and these other neuropathies may clarify the role of serum factors in acquired inflammatory diseases of the PNS.

Key-Words: Guillain-Barré – serum factors – demyelinating – neuropathies immunopathologic diseases.

Introduction

The Guillain-Barré Syndrome (GBS) is an acquired inflammatory demyelinating disease of the peripheral nervous system (PNS) of unknown etiology and pathogenesis. The presence of mononuclear inflammatory cells [5, 29] and similarities to experimental allergic neuritis (EAN) [3, 5], an experimental disease widely held to be T-cell mediated (Type IV immunopathogenic mechanism [15, 33], have led most investigators to feel that GBS is a T-cell mediated autoimmune disease [3, 4]. Such a view has been reinforced by studies describing in vitro cell-mediated immune reactivity to whole PNS myelin [68] or to components of PNS myelin such as the P2 (also called P1L) basic protein [1, 82] and by cytotoxic effects of blood mononuclear cells from patients with GBS when incubated with myelinated PNS cultures [3]. In contrast, we [102] and others [33] have not been able to confirm heightened in vitro cellular reactivity to P2 protein, albeit not of human origin, by blood lymphocytes of GBS patients. The in vitro...
cytotoxic effect of GBS mononuclear cells in rodent PNS cultures would represent a somewhat unlikely T-cell killing across histocompatibility barriers [17] and could reasonably be interpreted as being evidence of either natural killer (NK) [79] cell or an antibody determined cell-mediated cytotoxic (ADCC or K cell) immunopathologic reactions [62]. At the same time there has been developing a body of data from studies of sera from experimental animals and with humans that supports the concept that humoral (serum) factors may be important in GBS. It is the purpose of this article to review the evidence for the role of serum factors in the pathogenesis of GBS.

Experimental Antisera

Sera from animals with EAN induced by sensitization with whole PNS (EAN 

\(_{PNS}\) binds to the surface of cultures Schwann cells [49] and causes in vitro demyelination of PNS cultures [99]. EAN 

\(_{PNS}\) serum also causes demyelination after intraneural injection into rat sciatic nerve as evidenced by clinical weakness, electrophysiological conduction block and pathological demyelination [28, 70, 73]. The lesions produced by intraneural injection develop rapidly and inflammatory cells are not present in the early stages of the demyelinating lesion [70, 92], but antisera raised to myelin basic protein (MBP) or P 

\(_2\) protein, constituents of Schwann cells (PNS myelin) do not bind to Schwann cell surfaces [38, 41, 55], cause in vitro PNS demyelination [56] or cause in vivo demyelination after intraneural injection [65, 73]. The demyelinating lesions, which are reversible (remyelination), [70, 72, 92] have striking similarities to GBS. Absorption studies of such sera [49] and studies of antisera raised to galactocerebroside (GalC) [49, 59, 78, 92] indicated that most, if not all, of these properties of EAN 

\(_{PNS}\) antisera are determined by anti-GalC antibodies. The demyelinating [73, 92] or Schwann cell cytotoxic reactions [2] are heat labile and likely complement mediated. Of equal importance, about two thirds of rabbits repeatedly sensitized with bovine [76] or synthetic [75] GalC develop a demyelinating neuropathy with flaccid quadriparesis and slowing of nerve conduction. Neuropathologically, the demyelinating lesions are most marked in the roots and dorsal root ganglia. The central nervous system (CNS) is not affected. GalC is an important component of PNS myelin. GalC also is found in CNS myelin and indeed anti-GalC antibodies: a) bind to oligodendrocytes in culture [30, 38, 49, 55]; b) cause complement mediated lysis of oligodendrocytes [30]; c) cause in vitro myelination inhibition and demyelination [18, 22, 25]; and d), cause demyelination of guinea pig optic nerve following intraneural injection [81]. Serum from some animals with experimental allergic encephalomyelitis (EAE) induced with whole CNS have high anti-GalC titers and share these in vivo and in vitro properties with anti-GalC antisera [8, 25, 49, 74, 92]. The sparing of the CNS and relative sparing of the distal PNS in the GalC EAN rabbit may relate to permeability of the blood nerve barrier in some rabbits in the dorsal root ganglia and the roots [61, 97, 98]. Thus, depending on local factors, including vascular integrity, a CNS or PNS specific disorder could result from antibodies to a common determinant.

Naturally Occurring Diseases of Animals

There are several disorders of animals which have similarities to GBS in man including coonhound paralysis [16], acute canine idiopathic polyneuropathy (ACIP) [58], cauda equina syndrome of horse [35] and Marek's disease [88]. There are few studies of the serum of animals with these disorders. Sera of cattle with cauda equina syndrome have been reported to contain antibodies to myelin P, protein [35] and sera from chickens with Marek's disease have been reported to have antimyelin antibodies [88]. Recently, it has been demonstrated that the sera of dogs with ACIP causes mild but definite demyelination after intraneural injection in rat sciatic nerve [11]. Whether the demyelinating factor in the sera of these dogs is an antibody and if an antibody to what PNS constituent will be the subject of future studies.

Human Serum

Studies of GBS patients' sera for in vitro evidence of PNS myelin or Schwann cell specific immunologic reactivity have been controversial. Serum Ig from GBS patients binds to myelin [50, 53, 59, 95] and Schwann cell surfaces [37, 39] but disease specificity has not been demonstrated. It has been suggested that Ig normals and GBS patients bind to myelin nonspecifically through the Fc portion of Ig but that in addition, GBS Ig binds to myelin via the Fab portion [59]. The latter binding would be a true antigen-antibody reaction. We [102] and others [32, 33] have found little evidence for increased serum anti-P, or BP binding in GBS. In preliminary experiments using several highly sensitive assays that detect anti-GalC antibodies [24, 69, 85], we have not been able to demonstrate significant anti-GalC

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