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PATHOGENESIS OF CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

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1. ABSTRACT

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a term applied to a spectrum of immune-mediated demyelinating neuropathies that are heterogeneous in clinical manifestations and probably in pathogenesis. Although histopathologic studies of CIDP have been complicated by a relapsing course of the inflammatory reaction and its predominance in proximal nerve segments, many clues point to involvement of both cellular and humoral immune factors in the pathogenesis. Uncertainties remain regarding the provoking antigen(s) and location of the initial T cell activation. Breakdown of blood nerve barrier by activated T cells and its cytokines is followed by a local intraneural immune response with recruitment of macrophages and secretion of toxic factors, which cause damage to the myelin and axons. Activated T cells may also induce B cells to produce antibodies against nerve/ myelin antigens. This review summarizes our current knowledge of the immunopathogenesis and insight from animal models of CIDP.

2. INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an uncommon but treatable cause of neuropathy affecting 1-2 per 100,000 people(1, 2). Its prevalence may be underestimated because of its clinical heterogeneity, multifocality, predilection for proximal nerve segments and lack of sensitivity of electrophysiologic criteria to detect demyelination (3). CIDP typically involves both sensory and motor fibers, and has a predilection for nerve roots, plexi and proximal nerve trunks, causing symmetrical proximal and distal weakness.

Proposed criteria for the diagnosis of CIDP includes: 1) symmetrical proximal and distal weakness with altered sensation; 2) course of illness that is either relapsing-remitting, or progressive with maximal deficit at 8 weeks or longer after the onset of symptoms; 3) hyporeflexia or areflexia; 4) elevated CSF protein with minimal pleocytosis; 5) features of demyelination in electrophysiologic studies, including partial conduction block, slowing of conduction velocity and prolonged distal and F wave latencies. Pathologic evidence of demyelination is also required in the American Academy of Neurology (AAN) criteria for the diagnosis of CIDP (4), but not in more recently proposed criteria (5). However, more than half of CIDP patients have atypical features, including predominantly distal involvement, purely sensory neuropathy, marked asymmetry and associated cranial nerve and CNS demyelinating disease. The clinical course of CIDP is also heterogeneous. It may be slowly progressive, relapsing-remitting, monophasic or progressive after an initial remitting- relapsing phase (6-8).

3. PATHOLOGY

Pathologic hallmarks of demyelination such as segmental demyelination and remyelination, thinned myelin sheaths, and onion bulb formation may or may not be seen in the sural nerve biopsy as the disease is often multifocal or motor predominant. In addition, demyelination at proximal sites will not be detected by a sural nerve biopsy. Assessment of 95 sural nerve specimens of CIDP patients showed purely demyelinating lesions in 68, mixed axonal and demyelinating features in 20 and predominantly axonal lesions in 5 (6). Another study showed demyelinating features in only 48% of patients with CIDP (9).

Axonal degeneration occurring in the course of a demyelinating neuropathy has been attributed to a

bystander effect in inflammatory foci, immune attack directed towards epitopes on axons or secondary to increased endoneurial pressure. Axonal loss has a greater long-term prognostic impact than active demyelination, inflammatory infiltrates, or onion-bulb formations (6).

Inflammatory infiltrates are typically more prominent in proximal nerve trunks or spinal roots. T cell and macrophage infiltrates are seen in the endoneurium of sural nerves from patients with CIDP (10), with macrophages phagocytosing myelin fragments and Schwann cell membranes. T cells may also be seen within the basement membrane of fibers in contact with macrophages (11). However, inflammatory cells are frequently absent in sural nerve biopsy. In one study, increased endoneurial cellularity with perivascular predominance was seen in only 18 of 95 sural nerve biopsy samples, with four specimens showing prominent inflammatory infiltrates of CD4 and CD8 T lymphocytes, macrophages, and a few B cells (6).

4. ETIOLOGY

Evidence suggesting an autoimmune basis for CIDP includes its resemblance to Guillain-Barré syndrome (GBS), its response to immunomodulatory treatments, and development of a chronic relapsing form of experimental autoimmune neuritis (EAN) with electrophysiologic and pathologic resemblance to CIDP in animals (12, 13). Molecular mimicry may play a role in the immunopathogenesis of CIDP (14), but the antigen involved has been elusive so far. Unlike GBS, a link with antecedent infections and the occurrence of CIDP has not been well established, although 32 percent of 92 patients with CIDP mentioned a history of preceding infection (15). The rare association of CIDP with melanoma raises the possibility of common antigens shared by melanoma cells and peripheral nerve myelin such as gangliosides (16, 17). Whether there is a genetic predisposition to the development of CIDP has not been proven, at least from studies of HLA typing (18, 19).

5. IMMUNE MECHANISMS IN CIDP

5.1. Cellular immunity

The initial events in T cell activation consist of: 1. Recognition of processed immunogenic material (possibly Superantigens) presented with major histocompatibility complex (MHC) molecules by antigen presenting cells (APC), 2. Interaction of antigen nonspecific co-stimulatory molecules B7-1 and B7-2 on the APC with CD28 and CTLA-4 receptors on T cells; 3. Adhesion and extravasation of systemically activated T cells; and 4. Local amplification of the immune response within the nerves (14). Activated T cells are found in nerve biopsies of CIDP patients (6, 20, 21). However, the antigenic targets of aberrant T-cell responses, and dominant T-cell receptor (TCR)-Vbeta utilization remain unidentified (14, 22). Gammadelta T cells, which are capable of recognizing non-protein antigens such as gangliosides, were observed in 14 of 20 CIDP nerve biopsy specimens (23). Whether the initiation of these early events takes place in lymphoid organs or locally within the peripheral nerves in CIDP is unclear. Increased expression of MHC like molecule CD1a and CD1b by endoneurial macrophages and possibly Schwann cells in nerve biopsies of CIDP patients suggest that they act as APCs particularly in regards with non-protein antigens (21, 24). Moreover, the expression of CD58 molecule (LFA-3) by Schwann cells in CIDP nerves further supports the concept that they participate as accessory cells in T cell activation (24). The expression of CD58 by Schwann cells in CIDP may increase their susceptibility to lysis by cytotoxic T cells (25).

In addition to the antigen-specific signal via T cell receptors, complete activation of T cells requires signaling via co-stimulatory molecules B7-1 and B7-2. Antigen presentation in the presence of B7-1 molecules involves interaction with CD28 receptors, which causes T cell differentiation to Th1 phenotype with expression of IL-2, IFN-gamma and TNF-alpha whereas presentation in association with B7-2 induces Th2 phenotype with predominant expression of IL-4 (26, 27). The latter involves CTLA-4 receptors and causes peripheral T cell tolerance (28). Antigen presentation in the absence of B7 molecules may induce anergy or immunosuppression. Consistent with the above concept, there is a preferential upregulation of B7-1 rather than B7-2 in CIDP nerves (29).

Lymphocyte migration across the blood nerve barrier (BNB) depends on the interaction between molecules on lymphocytes and adhesion molecules on endothelial cells. At least 3 families of adhesion molecules are involved in leukocyte-endothelial interaction: selectins, integrins and members of immunoglobulin family (30). Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha) promote the breakdown of the BNB by upregulation of adhesion molecules (31, 32). Matrix metalloproteinases (MMPs) such as MMP-9 and MMP-2 are also implicated in degradation of BNB (33-35). MMP-2 has been shown to mediate the migration of T cells across a blood-brain-barrier model (36, 37), whereas MMP-9 functions as an effector molecule of extravasation and early interstitial infiltration in inflammatory neuropathies. Not surprisingly, MMP-2 and MMP-9 were found to be upregulated in nerves of CIDP patients with T cells as the predominant cellular source (35).

Further recruitment of mononuclear cells across the BNB is facilitated by chemokines, which are chemoattractant cytokines. Alpha Chemokines (CXCL9 and CXCL10) predominantly recruit T lymphocytes whereas beta chemokines (CCL2, CCL3, CCL4 and CCL5) recruit both T lymphocytes and monocytes (38). Chemokines also have other

functions such as activation of macrophages, induction of nitric oxide synthesis, and differentiation of naive T cells (38). CCL3, CXCL9 and CXCL10 were elevated in the CSF of CIDP patients compared to controls (39). A recent study identified perineurial endothelial cells in peripheral nerves as the source of CXCL10 in patients with CIDP. Quantitative analysis revealed that CXCR-3 (the receptor for CXCL10) was upregulated by T cells in inflammatory neuropathies (40). These findings confirm the significant role of chemokines in the pathogenesis of CIDP.

Once there is ample mononuclear infiltration, peripheral nerve injury and demyelination can occur by multiple mechanisms. Activated Th1 cells secrete interleukin-2, TNF-alpha, and interferon-gamma (IFN-gamma), which activate cytotoxic $CD8^+$ cells and macrophages- the principal effector cells in immune-mediated demyelination. Aside from elaborating cytotoxic compounds and cytokines such as TNF-alpha, macrophages may penetrate seemingly intact myelin sheaths and strip myelin from the axonal surface (11, 41, 42). Macrophages in actively demyelinating lesions in CIDP nerves had upregulated TNF-alpha immunoreactivity (42). TNF-alpha and IFN-gamma have been shown to act synergistically to decrease the Schwann cell viability and to downregulate the expression of myelin associated glycoprotein (43, 44). It has been reported that elevated serum TNF-alpha concentrations in a subgroup of CIDP patients is associated with severe clinical disability, subacute progression and diffuse demyelination on the nerve conduction study (45). Another group of molecules implicated in demyelination are the eicosanoids, including prostaglandin E2 (PGE2). Up-regulation of COX-2 protein and mRNA was seen in CIDP nerves. The ability of glucocorticoids to inhibit the stimulated production of TNF-alpha and PGE2 in macrophages may explain at least partially their therapeutic benefits in CIDP (46).

Factors leading to the termination vs. persistence of the immune response remain poorly understood. It has been proposed that activated T cells can be removed by two mechanisms: activation-induced apoptosis via Fas/Fas L system, and death by neglect due to cytokine withdrawal (47, 48). Work by Wohlleben *et al* suggests that FasL-expressing Schwann cells may contribute to the elimination of autoreactive T cells (48). It is possible that impaired Fas/Fas L interaction results in the persistence of inflammatory reaction and chronic progressive course in CIDP. NK T cells may also play a local regulatory role in CIDP lesions. There was expression of NK invariant V alpha24J alphaQ TCR chain and IL4 mRNA in CIDP nerve samples, although the precise role of NK T cells in CIDP remains to be elucidated (49). Although remission is generally associated with increased production of IL-4, IL-10 and TGF-beta, the finding of higher percentage of $IL\text{-}4^+$/$IFN\text{-}gamma^-$ $CD4^+$ cells in the peripheral blood of CIDP patients (50) indicates that the dichotomy between Th1 and Th2 cells in the pathogenesis and recovery of autoimmune diseases is oversimplified.

5.2. Humoral immunity

Immunoglobulins and complement deposits have been observed in CIDP nerve biopsies (51, 52). Preexisting damage to BNB by the T cells or cytokines is required for antibody-mediated demyelination (53). Proposed mechanisms of antibody-mediated demyelination include direction of macrophages to autoantigens (through Fc receptors), facilitating phagocytosis by opsonization of target structures, and activation of the complement pathway (54). Antibodies against Schwann cell leading lamella were found in 26% of CIDP patients (55). Yan *et al* have shown that serum or IgG of CIDP patients could cause demyelination when given by intraneural injection (56). In another study by the same group, anti-P0 antibodies were found in a subset of CIDP patients, and these antibodies caused conduction block and demyelination when injected intraneurally (57). The role of antibodies against PMP22 in CIDP remains controversial (55, 58-60).

Other probable target antigens include myelin gangliosides and other glycolipids. Anti-GM1 antibodies were found in 15% (6/40), and antibodies against LM1 and chondroitin sulfate were present in 5-10% of CIDP patients (61). In another study, anti-GM1 antibodies were found in 23% of CIDP patients and were associated with predominant motor involvement (62). The low prevalence of these antibodies may reflect the underlying heterogeneity of CIDP or low specificity of these autoantibodies (Figure 1).

6. ANIMAL MODELS OF CIDP

6.1. Chronic (EAN)

Since the first description by Waksman and Adams (63), EAN has been used extensively to investigate the immunopathogenesis of autoimmune demyelinating neuropathies. Immunization with purified P0, P2, PMP22 and MAG has induced conditions similar to GBS and CIDP in rodents (64-67). The disease is monophasic with spontaneous recovery with a few exceptions. In the study by Brosnan *et al.*, 30% of Lewis rats developed chronic EAN(68). The clinical severity of EAN is generally milder in mice than in rats, although it can be enhanced by a combination of peripheral nerve myelin in CFA and pertussis toxin plus IL-12 treatment in SJL/J mice (69).

Immunization with myelin followed by low dose cyclosporin A (CsA) treatment induced a mild and relapsing form of EAN in the Lewis rats while higher doses of CsA attenuated the disease. This observation suggests that high dose CsA inhibits the effector T cells thus suppressing the EAN. In contrast, the incomplete suppression of effector T cells plus the

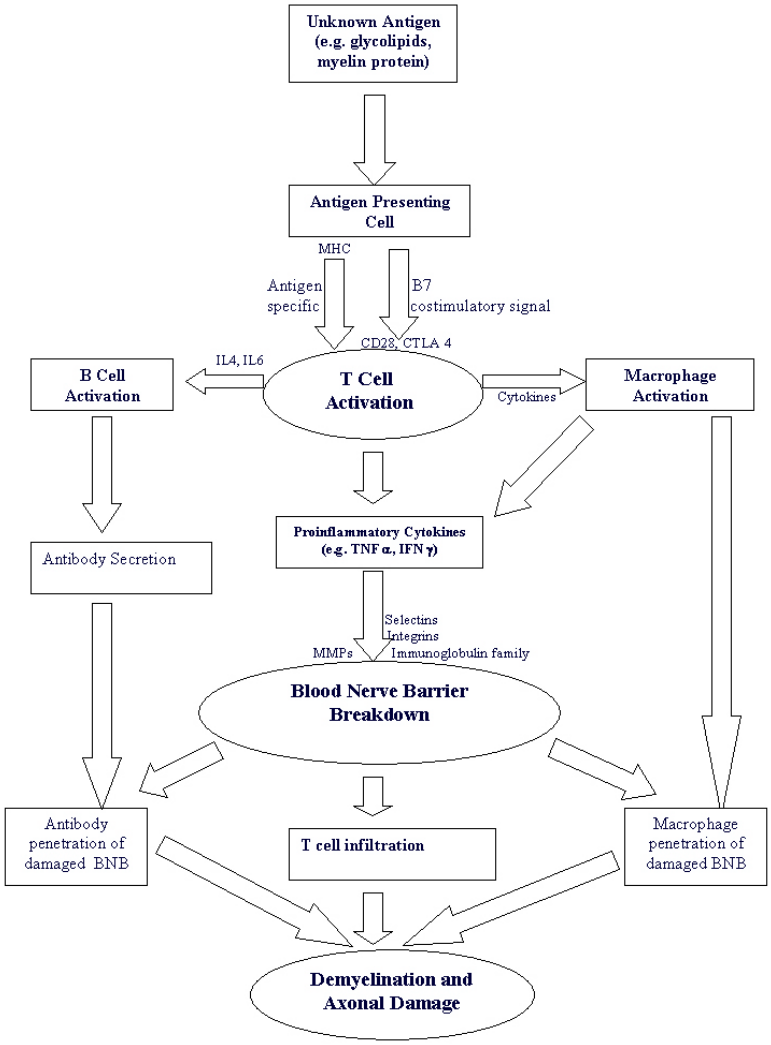

Figure 1. Schematic diagram summarizing events in the immunopathogenesis of CIDP.

inhibition of T cell apoptosis by low doses of CsA lead to a relapsing form of EAN (70). A model of chronic EAN can also be induced in rabbits immunized with a higher dose of bovine peripheral myelin than that used to induce acute EAN; 4 of the seven affected animals developed a relapsing form while the remaining 3 had a progressive course (13). Experimental evidence from studies in EAN suggests that the sequence of pathogenetic events in CIDP resemble that in chronic EAN except for the triggering antigen, which is still unknown in CIDP.

6.2. Spontaneous autoimmune peripheral polyneuropathy (SAPP)

The nonobese diabetic (NOD) mouse strain is a model of type 1 diabetes, but it also has the propensity to develop other autoimmune diseases. In an effort to investigate the role of B7-2 in type 1 diabetes, NOD mice were bred onto the B7-2 deficient background. Elimination of B7-2 prevented the development of insulitis and diabetes, but unexpectedly, all female and one third of male mice developed a demyelinating neuropathy beginning at 20 wks of age and did not recover spontaneously. There was heavy infiltration by $CD4^+$, $CD8^+$ T cells and dendritic cells in peripheral nerves and dorsal root ganglia. There was overexpression of B7-1 by the APC. Morphologic and sciatic nerve conduction studies confirmed the presence of a demyelinating neuropathy with varying axonal degeneration. Thus, the B7-2 deficient NOD mouse constitutes the first model of a spontaneous autoimmune neuropathy mimicking CIDP clinically, electrophysiologically and histologically. The disease was reproduced by treatment of NOD mice with antibody against B7-2, or by transfer of $CD4^+$ T cells into NOD.SCID recipients but not by sera from SAPP animals (71).

Exactly how the elimination of B7-2 triggers the polarization of autoimmunity from pancreatic cells to peripheral nerves is unclear. It is possible that the unopposed upregulation of B7-1 in the spleens of B7-2 deficient NOD mice promotes activation of myelin-reactive T cells or results in the perturbation of

regulatory T cells. This animal model has significant implications: 1) autoimmune prone individuals may develop different autoimmune diseases depending on the co-stimulatory milieu, and 2) caution must be exercised in the use of co-stimulatory blockade in the clinical setting.

7. PERSPECTIVE

A better understanding of the molecular pathogenesis of CIDP is necessary to develop novel treatments for this disease. Potential new therapeutic strategies include TNF-alpha inhibitors, interferons, blockade of the adhesion molecules, and induction of T cell apoptosis and inhibition of macrophage function. To this end, pilot studies of etanercept and interferon-beta1a have shown promising results in CIDP (72, 73). Further research is warranted to determine the mechanisms permitting the persistence of the immune response in CIDP versus its termination in GBS.

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