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Update on Guillain-Barre Syndrome-Like Conditions in Animals

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Abstract

Disease conditions, including Coonhound paralysis, acute canine polyradiculoneuropathy (ACP), and cauda equina neuritis do occur in animals naturally from time to time. The experimental induction of paralysis in chickens with certain strains of *Campylobacter jejuni*, and the recent observation of *Toxoplasma*-induced ACP raise the possibility that peripheral nerve disease via immunologic mechanisms, induced by microorganisms, may occur in animals naturally. Experimental studies have indicated that antigens responsible for production of cross-reacting antibodies that cause neurological injury may be present in unrelated bacterial pathogens such as *C. jejuni* and *Brucella melitensis*. Further studies are required to determine if antibodies against *C. jejuni* can damage human neural cells including oligodnendroglial cells, the cell type responsible for myelin production in the central nervous system.

Introduction

Guillain-Barré syndrome (GBS) is an acute disease of the peripheral nervous system of humans, characterized by ascending paralysis, conduction block with segmental demyelination of the nerves, macrophage and lymphocytic infiltration of the nerves, and elevated protein with no cells or very few cells in the cerebrospinal fluid (Constantinescu et al. 1998). Descriptive accounts on GBS, including history, clinical, pathological, and epidemiological aspects are given by Hughes (1990), Ropper et al. (1991), and Hughes et al. (1997). If full credit were to be given to those clinicians who first recognized and described this paralytic disorder, then its name might properly be Landry-Guillain-Barré-Strohl syndrome (Steinberg 1995). The diagnostic criteria for this idiopathic neuropathy have been outlined by Asbury et al (1978, 1981, 1990), and these include more or less symmetrical paresis, and a loss of myotatic reflexes (Van der Meche et al. 1997). These symptoms may be caused by inflammatory demyelination, axonal degeneration, or both (Hughes and Rees 1997). Motor, sensory and autonomic nerves supplying the limbs are affected invariably, but respiratory muscles, facial, bulbar, and ocular motor nerves may be involved (Hughes and Rees 1997). GBS has been shown to be associated with viral or bacterial infections, including Campylobacter jejuni (Kaldor and Speed 1984, Hariharan et al 1996), Borrelia burgdorferi (Sigal and Tatum 1988), Brucella melitensis (Namiduru et al. 2003), or infection with the protozoan parasite, Toxoplasma gondii (Pascual et al. 1984, Bossi et al. 1998), or following vaccinations, including rabies (Hemachudha et al 1988) and swine influenza (Langmuir et al 1984), or surgical procedures (Aranson and Asbury 1968).

The present review is an attempt to update the one published 12 years ago by Hariharan et al. (1999) on natural and experimental animal models of GBS, and includes recent findings, including possible role of Toxoplasma gondii and Brucella melitensis in causing immunologically mediated nerve injury in animals.

Natural animal models

Some naturally occurring animal diseases with varying degrees of resemblance to GBS have helped to understand immmunopathology and other aspects of human disease. Coonhound paralysis (CHP), first described in 1954 is a neurological condition of dogs that resembles GBS of humans, and it occurs in coonhounds in 1-2 weeks following a raccoon bite or scratch (Kingma and Catcott 1954). It was identified pathologically as acute canine polyradiculoneuritis by Cummings and Haas (1967, 1972), who described the clinical and pathological features. The initial symptoms are weakness and hyporeflexia in the hind limbs. Paralysis progresses rapidly, resulting in flaccid symmetric quadriplegia. The affected animals remain afebrile, and at the peak of their illness, there may be complete absence of spinal reflexes, facial weakness and labored respiration. Electromyographic findings include evidence of denervation. Deaths have occurred due to respiratory failure. As in the case of GBS, CHP is characterized by motor conduction delay and CSF albuminocytologic dissociation in affected dogs. Affected roots and nerves contained mononuclear cell infiltrates, segmental myelin changes and axon degeneration. However, axon damage is a more consistent finding in CHP than in GBS (Cummings et al 1982).

Idiopathic acute polyradiculoneuropathy (ACP) is the most commonly recognized peripheral neuropathy in dogs, and it closely resembles the acute axonal or

intermediate forms of GBS in humans (Cuddon 1998). ACP has an acute onset with less than 21 days to the time of most severe effect. The diagnosis can be confirmed by electromyography, indicating denervation of affected muscles, and by nerve conduction velocity measurements which will reveal slowed conduction in affected segments (Northington et al 1981, Northington and Brown 1982). The underlying cause of the neuropathy in dogs diagnosed with ACP is obscure, and recovery can take several weeks (Northington et al 1981, High 1996). ACP has been reported in dogs after rabies vaccination (Collins 1994). It has been suggested that an infectious agent or an antigen that gains entry into a susceptible host could trigger an autoimmune process that damages Schwann cells, resulting in demyelinating neuritis (Hawe 1979). In Hawe's (1979) report on ACP, the condition was differentiated clearly from other causes of diffuse lower motor neuron diseases such as botulism. Peripheral nerve dysfunction as shown by electrophysiological examination, is not uncommon in dogs affected with type C botulism (van Nes and van Spijk 1986), the type than affects a variety of animals (Hariharan and Mitchell 1977). It is interesting to note that a variant form of human botulism was initially diagnosed as GBS because of the demyelinating polyneuropathy (Sonnabend et al. 1987). Very recently, it has been documented that ACP in some dogs, like GBS in some humans, may be triggered by Toxoplasma gondii infection (Holt et al. 2011).

Paralytic illnesses resembling human GBS have been reported in monkeys (Schultz 1987, Alford and Satterfield 1995). The disease reported by Alford and Satterfield (1995) in a chimpanzee was characterized by ascending, symmetrical, monophasic flaccid paralysis, with albuminocytologic dissociation in CSF. Partial recovery followed supportive treatment, but muscle atrophy was evident after one month, and it took several months for the chimpanzee to regain full mobility. The cause was unknown, but prior to the condition the animal was revaccinated for rabies, and a severely abscessed tooth was extracted.

Decades ago, Marek's disease in chickens has been noted as a natural model for GBS. The similarity of the pathogenesis of this disease in chickens to GBS in humans is with regard to the autoimmune response to myelin and peripheral nerves. However, neuropathy in Marek's disease is initiated by the establishment of viral infection in neuronal supporting cell, and subsequent demyelination due to a specific immune response to viral-induced antigens on these cells (Pepose et al. 1981, Stevens et al. 1981). Idiopathic polyneuritis with accompanying paralysis, demyelination and invasion of nerve fibres with lymphocytes and macrophages, without any evidence of antecedent viral infection or any other known cause has also been reported in chickens (Biggs et al. 1982).

GBS-like disease conditions have also been reported in other animal species. One of these is cauda equina neuritis in horses, in which a chronic polyneuritis affects the sacral and coccygeal nerves, and sometimes the cranial nerves as well. The disease is characterized by the appearance of a series of neurological signs, which includes paralysis of the tail, bladder, and rectum, and in some cases, hind legs, as well. The nerve bundles of the cauda equina may have swelling, and varying stages of inflammation, beginning with concurrent demyelinaion, degeneration and cellular infiltration (Greenwood et al. 1973, Manning and Gosser 1973). Kadlubowski and Ingram (1981) noted the presence of circulating antibodies to myelin protein P2 in neuritis of the cauda equina of horses. The causes of cauda equina are not known, but upper respiratory disease involving streptococci may be a factor (Martens et al. 1970).

Polyradiculoneuritis similar to GBS has also been diagnosed in a goat. There was progressively developing ataxia, and lesions included segmental demyelination, Schwan cell proliferation, and mononunuclear inflammatory cell infiltration in spinal nerve roots as well as in the peripheral nerves of the fore and hind limbs (MacLachlan et al. 1982).

Experimetal models:

Holmes and co-workers (1979) experimentally reproduced coonhound paralysis in one of a pair of coonhounds, injected with 1.0 ml of a pool of raccoon saliva. The onset of paralysis of hind limbs occurred 9 days later, and progressed rapidly to involve the forelimbs, neck and tail. The course of the disease was quite comparable to GBS. By 48 hours the dog was tetraplegic and areflexic. Respirations weakened at 72 hours and the animal was placed on a respirator. Reduced ulnar conduction was recorded on day 5. The dog was able to stand after 6 weeks, and ability to walk short distances returned by 8 weeks.

An animal model of GBS, termed experimental autoimmune ("allergic") neuritis (EAN), was first described by Walksman and Adams (1955, 1956), who produced the condition in rabbits, guinea pigs and mice by injecting peripheral nerve emulsions in complete Freund's adjuvant. Later, other workers used rats with success, and mycobacteria was not required in the adjuvant for inducing EAN (Levine an Wenk 1963). Subsequently, Lewis rats were found to be more susceptible to EAN, and the Lewis rat model became a widely accepted animal model for GBS (Smith et al. 1979, Saida et al 1981). Clinically, EAN is an acute disease appearing two weeks following

immunization and consisting of ataxia and ascending limb weaknss (Steiner and Abramsky 1985). In this model, the rats showed weakness of all extremities, leg splaying, inability to hold head, facial weakness with loss of blinking, and labored shallow respirations. Hind leg dragging and unusually flaccid and weak forelimbs were seen in some animals. EAN lesions are characterized by infiltration of lymphocytes and other mononuclear cells, and demyelination in the areas of inflammation (Smith et al. 1979, Steiner and Abramsky 1985). EAN has been produced by injection of myelin of rat, rabbit, bovine or human origin. It can also be produced by adoptive transfer of autoimmune T cells (AT-EAN) reactive with myelin proteins such as P2 or P0 (Hartung et al. 1988, Archelos et al. 1994). It is possible to produce a mild and entirely demyelinating form of actively induced EAN by immunization of rats with small dose of myelin, and a more severe variety with extensive demyelination and significant axonal damage in animals that received a large dose of the immunogen. In AT-EAN, the injection of myelin protein P2-specific lymphocytes into Lewis rats can produce either fulminant neuritis characterized electrophysiologically by conduction failure that resembles acute nerve transection and morphologically by axonal degeneration and prominent endonurial edema (high cell dose), or upon transfer off a smaller number of cells a milder condition with late onset of signs of conduction slowing and predominant demyelination (Hartung et al. 1988). The role of humoral factors in the pathogenesis has also been studied in experimental animals. For instance, intraneural injection of serum from animals with EAN has been shown to transfer demyelinating activity to normal recipient animals (Saida et al. 1978, Summer et al. 1982a). Antiserum against galactocerebroside, a major component of peripheral nerve myelin, has also been shown to induce demyelination on intraneural injection (Saida et al. 1979). Later, serum from GBS patients was shown to produce similar effect on sciatic nerves of rats, with acute conduction block and demyelinating activity. Demyelination appeared to evolve both by vesicular disruption and by macrophage mediated myelin stripping (Saida et al. 1982, Sumner et al. 1982b, Harrison et al. 1984). More recently, systemic administration via intraperitoneal route of serum from GBS patients into mice has been shown to produce GBS-like signs, and changes in peripheral nerve function (Noterman et al. 1992, van den Berg et al. 1994). The animal models helped in elucidating the mechanisms involved in GBS, as well as in developing experimental approaches to treat autoimmune neuritis. Interestingly, EAN can be totally prevented in rats treated with an immunomodulator linomide (Karpati et al. 1998). Therapeutic approaches in humans include use of corticosteroids for macrophage depletion and, plasma exchange, the later being in common use for treatment of GBS (Ropper et al. 1991).

Campylobacter jejuni and GBS

The initial reports of the association between the leading diarrheal pathogen Campylobacter jejuni and GBS were published during 1982-1984 (Kaldor and Speed 1984). Evidence of preceding C. jejuni infection was found in 38% of 56 GBS patients in a retrospective study conducted by the above authors in Australia. Since then there have been many reports from different parts of the world documenting a strong association between infection with C. jejuni and GBS. In a study conducted from 1990 to 1996, 44% of 205 Japanese GBS patients had serological evidence of recent C. jejuni infection, compared with 1% in healthy controls (Saida et al. 1997). Besides serological evidence of C. jejuni infection, investigators from several parts of the world have also succeeded in isolating C. jejuni from the stools of patients with GBS at the onset of neurologic symptoms (Allos 1997). Hariharan et al. (1996) found three (38%) of 8 GBS patients in India culture positive for Campylobacter jejuni, the rate being within the range of culture-positive GBS cases in other parts of the world (Allos 1997).Two of the three culture-positive GBS patients in the above study (Hariharan et al. 1996) had a history of antecedent diarrhea. A positive C. jejuni stool culture and a history of enteritis preceding GBS are significant supporting evidence, though serological evidence alone may be non-specific, especially in older patients (Ropper et al. 1991).

Animal models of C. jejuni induced GBS

Infection with Campylobacter jejuni being one of the major predisposing factors in the development of GBS (Allos 1997, Nachamkin et al 1999) it became necessary to understand more on the mechanisms by which this bacterium induces GBS. There has been speculation that the lipopolysaccharde (LPS) of at least some strains of C. jejuni expresses a carbohydrate epitope shared with peripheral nerves. Human anti-GM1 antibodies have been known to cross-react with LPS from certain strains of C. jejuni (Wirguin et al. 1994). Carbohydrate mimicry of C. jejuni lipooligosaccharides is critical for the induction of anti-GM1 antibody and neuropathy (Shu et al. 2006, Perera et al. 2007). Isolates of C. jejuni from GBS cases may belong to any of the serotypes, though Penner serotype O:19 is the most common one among Japanese patients (Saida et al. 1997). Though in the United States about 75% of isolates of C. jejuni from diarrhea cases do not have GM1-like epitopes, all

GBS-associated isolates do possess GM1 or other ganglioside-like epitopes in the core region of LPS (Nachamkin et al. 1999). GBS cases with antecedent C. jejuni infection have been noted to be characterized by poor recovery and axonal damage as well (Vriesendorp et al. 1993, Drenthen et al. 2011).

Experimental animal models of bacteria-associated GBS included C. jejuni infection in the chicken exposed to a strain from a human case of GBS (Li et al. 1996). The strain used was of the serotype Penner O:19 from a patient who developed acute motor axonal neuropathy. Paralysis in chickens fed with the bacterial culture developed in 5-18 days, and sciatic nerves of some birds showed extensive Wallerian-like degeneration and paranodal demyelination. C. jejuni antiserum has been shown to produce reduced conductivity of the femoral nerve in rats (Murphy et al. 1999), axonal degeneration of the sciatic nerve in guinea pigs (Shu et al. 2007), and paralysis in rabbits (Komagamine and Yuki N 2006). Murphy (2003) observed that sera raised in rabbits against whole cell antigens of C. jejuni can damage human neural cell lines, including oligodendroglial cells, the cell type responsible for myelin production in the central nervous system (Miron et al. 2011). Further work is required on this aspect.

Brucella melitensis model in mice

Watanabe et al. (2005) observed flaccid limb weakness in mice immunized with Brucella melitensis, and the serum from immunized mice cross-reacted with GBS-associated C. jejuni, but not with non-GBS-associated C. jejuni. These authors found that a lipooligosaccharide of B. melitensis has a GM1 ganglioside-like structure. The cholera toxin B subunit, which binds to GM1 ganglioside specifically, reacted with the surface of B. melitensis. Two cases of human GBS associated with brucellosis have been reported (Goktepe et al. 2003, Namiduru et al. 2003).

Conclusion(s)

In conclusion, disease conditions resembling GBS, including CHP and ACP in dogs, and cauda equina neuritis do occur in animals naturally from time to time. The experimental induction of paralysis in chickens with certain strains of *C. jejuni* (Li et al. 1996), and the recent observation of *Toxoplasma* – induced ACP in dogs (Holt et al. 2011), raise the possibility that peripheral nerve disease induced by microorganisms may occur in animals naturally, and the need for further studies. Experimental studies such as the one by Watnabe et al. (2005) revealed that antigens responsible for production of cross- reacting antibodies that cause neurological injury may be present in unrelated bacterial pathogens such as *C. jejuni* and *Brucella melitensis*.

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