


Expanding the concept of inflammatory neuropathies

Inflammatory neuropathies include several clinical entities and constitute a major portion of peripheral neuropathies. Inflammatory neuropathies may be caused by immune-mediated mechanisms initiated by constituents of the peripheral nervous system. Among these neuropathies, Guillain–Barré syndrome and chronic inflammatory demyelinating polyneuropathy are especially well known. Although Guillain–Barré syndrome had been considered to be identical to acute inflammatory demyelinating polyradiculoneuropathy (Asbury, 1981), recent studies have added acute motor axonal neuropathy as a component of Guillain–Barré syndrome (Griffin et al., 1995; Hughes et al., 2005; Yuki and Kuwabara, 2007). In addition, investigations for anti-ganglioside antibodies have further widened the concept of Guillain–Barré syndrome (Kusunoki et al., 1999; Willison and Yuki, 2002; Kaida et al., 2008). Although chronic inflammatory demyelinating polyneuropathy usually manifests as a motor sensory neuropathy, a pure motor form, designated as multifocal motor neuropathy, and a pure sensory form, which is termed chronic immune sensory polyradiculopathy, may occur (Pestronk et al., 1988; Sinnreich et al., 2004). In addition to these mainly somatic neuropathies, the discovery of anti-ganglioside acetylcholine receptor antibodies has shed light on autonomic neuropathies in the field of immune-mediated neuropathies (Vernino et al., 2000). These immune-mediated neuropathies are caused by an abnormal
response to various underlying conditions affecting immune surveillance such as infection, certain types of vaccination, malignancy and graft-versus-host disease (Lisak et al., 1977; Langmuir et al., 1984; Hemachudha et al., 1988; Wen et al., 1997; Vernino et al., 2000; Hughes et al., 2005). Recently, the concept of immune-mediated polyradiculoneuropathy has been introduced as an occupation-associated illness among slaughterhouse workers exposed to porcine brain tissues (Lachance et al., 2010).

Connective tissue disorders may also cause neuropathy through inflammatory mechanisms. Vasculitis and subsequent ischaemia is a major component causing neuropathy through this mechanism. Peripheral neuropathy may appear as a systemic manifestation, while vasculitis confined to the peripheral nervous system without systemic manifestations has been reported (Kissel et al., 1985; Dyck et al., 1987). The concept for the underlying conditions inducing vasculitic neuropathy has also been widened. Infections—including human immunodeficiency virus, hepatitis B virus, hepatitis C virus and bacteria—malignancy and some drugs have been known as a background condition (Collins et al., 2005). Furthermore, impaired metabolic conditions such as diabetes mellitus have been demonstrated to show vasculitis (Said et al., 1994; Llewelyn et al., 1998; Dyck et al., 1999). Focal or multifocal neuropathy with predominant involvement of the proximal portion of the lower limbs is a well-known clinical subtype of diabetic neuropathy. This type of neuropathy is now considered to be inflammatory because vasculitis is observed in nerve biopsy specimens (Said et al., 1994, 2003, 2007; Dyck et al., 1999, 2002). A similar pattern of neuropathy has also been reported in patients without diabetes mellitus (Dyck et al., 2001, 2002). In addition to vasculitic neuropathy, Sjögren’s syndrome may be associated with various types of neuropathy including ganglionopathy (Griffin et al., 1990; Mori et al., 2005). Ganglionopathy may induce a wide range of clinical features, including sensory ataxia and pain (Koike and Sobue, 2008).

Against this background of a plethora of contexts in which inflammatory neuropathy may occur, Staff et al. (2010) from the Mayo Clinic, now report 33 patients who developed a peripheral neuropathy within 30 days of a surgical procedure and were considered to be free of nerve trauma (page 2866). The presence of neuropathy was confirmed by nerve biopsy in 21 of the cases, while the other 12 cases were suspected clinically. Peripheral nerve damage following surgical procedure is a well-known clinical problem and has been considered attributable to mechanical forces such as stretch, compression, contusion and transection. Through detailed analyses—including clinical characteristics, electrophysiology, MRI pathology of nerve biopsy samples and prognosis—the authors propose a new concept of ‘post-surgical inflammatory neuropathy’. This study may expand the concept of inflammatory neuropathies and advocates that neurologists should exercise more due care in the surgical and anaesthesiology fields than previously appreciated. It is interesting that most of the patients presented by Staff et al. (2010) manifested focal or multifocal neuropathy, and only 7 of 33 (4 of 21 biopsy-confirmed) cases showed a polyradiculoneuropathy pattern. Previously, clinical and pathological features of six patients with Guillain–Barré syndrome that occurred after surgery were reported (Arnason and Asbury, 1968). According to the review of 97 patients with Guillain–Barré syndrome in the Mayo Clinic, five cases were reported to occur after surgery (Wiederholt et al., 1964). Because Guillain–Barré syndrome may be considered by physicians for neuropathy occurring after some preceding events, focal features may have caused the inflammatory aetiology to be overlooked in these patients even though location of the neuropathy was spatially segregated from the site of surgery. Although surgery has been reported to be an antecedent event in some patients with neuralgic amyotrophy manifesting brachial plexopathy, a pathological correlation has not yet been assessed (van Allen et al., 2006).

This case series raises two important issues: (i) determination of mechanism of the neuropathies and (ii) the potential for treatment once an appropriate diagnosis has been made. The pattern of the neuropathies is focal or multifocal, similar to that of vasculitic neuropathy in most patients. Pathological findings of nerve biopsy specimens also support this mechanistic interpretation because findings suggestive or diagnostic of vasculitis, especially that of small vessels (i.e. microvasculitides) were observed. In addition, painful sensations, which are frequently reported in vasculitic neuropathies (Sugiuira et al., 2006), were described by most of the patients. However, features diagnostic of microvasculitides were not observed in four who manifested a diffuse pattern of neuropathy. Of these, Patient 7 showed marked demyelinating changes. Therefore, ‘post-surgical inflammatory neuropathy’ may include more than one disease entity. Assuming that the pathogenesis of neuropathy is related to ischaemia due to microvasculitis in the majority of patients in this series, it is unclear why the vasculitis seems to affect only the peripheral nervous system. For example, microscopic polyangitis, which preferentially affects small-sized vessels, involves a wide range of visceral organs other than peripheral nerves, such as the skin, respiratory tract, kidney and gut (Sugiuira et al., 2006). In contrast, the patients in this series seem to lack conspicuous signs and symptoms suggesting the involvement of other organs. They may have exhibited concomitant asymptomatic vasculitis in other organs, suggesting that post-surgical vasculopathy in non-neural tissues may exist but was overlooked. Therefore, a more careful examination may be required in postoperative patients. Alternatively, the inflammatory process may be similar to that of non-systemic vasculitic neuropathy (Dyck et al., 1987; Collins et al., 2003).

The cause of the inflammation is another issue to be clarified. In their discussion, Staff et al. (2010) suggested genetic predisposition, stress related to the surgical process, the transfusion of blood products, the effect of anaesthetics, diabetes mellitus, cancer or infection and a history of smoking as possible risk factors. It is interesting that lumbo-sacral radiculo-plexus neuropathy, which shows similar clinical and pathological findings to this case series, may occur in association with diabetes mellitus (Dyck et al., 1999, 2002). A large-scale epidemiological study, ideally prospective, of peri-operative conditions in patients receiving surgery will clarify the risk factors of ‘post-surgical inflammatory neuropathy’. This issue is important because it may identify possible candidates and provide sufficient informed consent before surgery. Furthermore, this information may lead to the prevention and early treatment of this neuropathy.
As for treatment, it is important to determine appropriate therapy for this neuropathy because it may evoke significant medico-legal problems. However, the response to immunomodulatory therapies, usually corticosteroids, should be evaluated carefully given the retrospective nature of the study. It may be difficult to determine the efficacy of potential therapies because this neuropathy may show a monophasic clinical course. Indeed, two of the biopsy-confirmed cases showed improvement without receiving immunomodulatory treatment. Therefore, the improvement after immunomodulatory treatment may merely reflect the natural course of the disease process. It is evident that prospective controlled, double-blind treatment trials are needed. Defining the clinical features, including its subtypes, is also important in this context. Physicians will be guided in the use of therapy, once the aetiology of this neuropathy is confirmed as immune mediated and the efficacy of immunomodulatory treatment demonstrated.

Staff et al. (2010) have provided a new concept of post-surgical neuropathy with an inflammatory aetiology. This study expands the concept of inflammatory neuropathies and suggests the need for increased involvement of neurologists in the surgical and anaesthesia fields than previously recognized. As the authors stress, it is important for physicians to recognize that not all neuropathies seen in the post-surgical setting are due to compression, transection or stretching. Introducing the concept of post-surgical inflammatory neuropathy is a contribution to classification in medicine and the management of patients cared for by physicians involved in many areas of medicine.

Funding

Funding for this article was provided by Ministry of Health, Labour and Welfare and the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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Advance Access publication September 20, 2010
doi:10.1093/brain/awq266

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