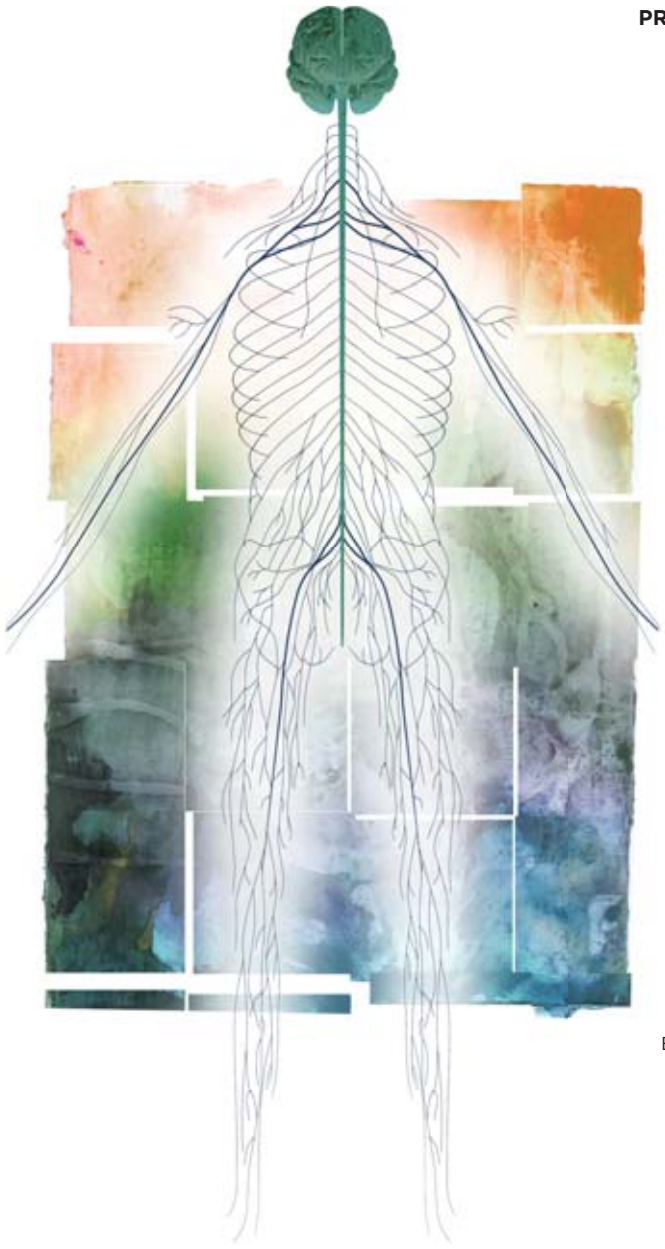
ANESTHESIOLOGY NEWS



Regional Anesthesia And the Patient With Preexisting Neuropathy

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The benefits of providing regional anesthesia for patients undergoing a variety of surgical interventions have been well established. What is less clear is whether individuals who manifest a preexisting neurologic condition in general, or a neuropathy specifically, are likely to benefit from the provision of regional anesthesia without incurring undue risk in terms of exacerbating that neuropathic process. This discussion highlights the current state of our understanding regarding the administration of peripheral nerve blocks (PNBs) or neuraxial anesthesia and analgesia in patients with preexisting neuropathies in terms of the influence, or lack thereof, of the anesthetic on the neuropathy.

Table 1. Types of Neuropathies

Diabetic peripheral neuropathy	Toxins
Renal failure	Malignancies
Hereditary conditions	Endocrine disorders
Entrapment neuropathies (CTS, UNS, brachial plexopathy)	Guillain-Barré syndrome
Alcoholic	Myotonic dystrophy
Porphyria	Myasthenia gravis
Nutritional deficiencies (vitamins B_{12}, A, E, B_1)	Multiple sclerosis (CNS)
Connective tissue disease	Amyotrophic lateral sclerosis
Infection	Charcot-Marie-Tooth
HIV-related neuropathy	Chemotherapy-induced

CNS, central nervous system; **CTS,** carpal tunnel syndrome; **PNS,** peripheral nervous system; **UNS,** ulnar nerve syndrome

Neuropathy is defined as "deranged function and structure of a peripheral motor, sensory, or autonomic nerve, involving the entire nerve or selected levels."[1] Four cardinal patterns of a peripheral neuropathy exist:

1. Polyneuropathy, defined as a generalized disorder of peripheral nerves;
2. Mononeuropathy, defined as disease involving a single nerve;
3. Mononeuritis multiplex, defined as inflammation of several separate nerves in unrelated parts of the body; and
4. Autonomic neuropathy, defined as a collection of syndromes and diseases affecting the autonomic neurons, either parasympathetic or sympathetic, or both.

Neuropathies may affect the peripheral and/or central nervous systems (CNS). The types of neuropathies commonly encountered in clinical practice are listed in Table 1.

Until recently, regional anesthesia provided for the patient with a preexisting neuropathy has received scant attention. A review of major reference works dedicated to regional anesthesia spanning 87 years, and more than 4,700 total pages, found only 5 pages wherein the issue of central neuraxial anesthesia or PNB was discussed in the context of neuropathy.[2-9]

In the 1953 book *Regional Block*, author Daniel C. Moore stated: "Whenever preexisting neurological disorders are present … the possibility of a medicolegal suit should be evaluated before administering a spinal, caudal, epidural or nerve block."[3] In the 1978 text *Epidural Analgesia*, Philip R. Bromage claimed, "Any postoperative neurological complications arising after regional anesthesia are likely to be attributed to the anesthetic. The nerve-blocking effects of subarachnoid and epidural anesthesia are so dramatic that it is perhaps natural to propose an etiology based on shallow assumptions of cause and effect."[4] Furthermore, Bromage wrote, "Although it is difficult to see how an epidural block could have an adverse effect on these conditions [preexisting neurologic diseases] the anesthesiologist will avoid the possibility of becoming involved in a post hoc, ergo propter hoc *litigation claim* should a natural exacerbation of the disease develop after the operation."[4]

In 1999, Brendan T. Finucane, in *Complications of Regional Anesthesia*, noted, "This dearth of information makes it impossible to define specific guidelines for the use of regional anesthesia in the patient with neuromuscular disease. It is also clear that in many neurologic and neuromuscular disorders, there may be a distinct advantage to the use of regional anesthesia over general anesthesia."[5] In the second edition of his book published in 2007, Finucane stated, "However a study of significant size to confirm or support the safety of regional anesthesia in these patients continues to remain scarce."[6] In 2007, Joseph M. Neal and James P. Rathmell, in *Complications in Regional Anesthesia & Pain Medicine*, stated,

"However, it has also been suggested that patients with preexisting neurologic deficits may be at increased risk as well. ... The presence of chronic underlying neural compromise secondary to mechanical, ischemic, toxic or metabolic derangements may place these patients at increased risk."[7] These authors were among the first to recognize the importance of the "double-crush phenomenon" in defining the etiology of several of these neurologic insults resulting following a regional anesthetic procedure in compromised neural states.

In scenario C, a nerve with a mild preexisting neuronal injury condition at 2 separate sites (X_1, X_2) may cause distal denervation (ie, double-crush). In scenario E, an axon with a diffuse preexisting underlying disease process (toxic, metabolic, ischemic) may have impaired axonal flow throughout the neuron, which may or may not be symptomatic but predisposes the axon to distal denervation following a single minor neural insult at site X (ie, double-crush).

Finally, in 2009, in *Cousins & Bridenbaugh's Neural Blockade*, Cousins et al stated, "The most conservative *legal approach* is to avoid regional anesthesia in these [ie, preexisting neurologic-disordered] patients. ... The decision to proceed with regional anesthesia in these [ie, high-risk] patients should be made on a case-by-case basis."[9]

Approach to the Patient With a Preexisting Neuropathy

The approach to the patient with a preexisting neuropathy presenting to the operating room as a potential candidate for regional anesthesia entails performing the preoperative evaluation and documentation standard for every patient. However, a special emphasis on the neurologic examination and on exercise tolerance is required. The respiratory and cardiovascular systems may be harbingers of a systemic neurologic disorder, and need to be evaluated especially carefully in the individual manifesting a peripheral neuropathic process. It is crucial to evaluate volume status, beat-to-beat heart rate variability, resting tachycardia, orthostatic hypotension, cardiac dysrhythmias, or the presence of impotence.

If regional anesthesia is determined as a prudent choice for these individuals, a comprehensive discussion detailing the relevant risks, benefits, and alternatives should be undertaken and documented. In fact, according to Brull et al, most academic anesthesiologists specializing in regional anesthesia are unable to provide patients with the actual substantive risks in most cases of regional block in non-neurologically impaired individuals.[10] This phenomenon is not unique to academic regional anesthesiology experts, but also extends, as expected, to a population of members of the American Society of Regional Anesthesia and Pain Medicine (ASRA).[11] In a survey of 3,732 ASRA members, with 801 (21.7%) responding, the likelihood of disclosing the pertinent risks associated with regional block to patients was again inconsistent—implying that under ideal circumstances, most anesthesiologists either are not cognizant of the relevant risks or do not discuss these risks at all times with all patients.

Table 2. Neurologic Complications After Regional Anesthesia[12]

Type of Block Anesthesia	Relative Incidence
Central neuraxial blocks	
Spinal anesthesia	3.78/10,000 (0.04%)
Epidural anesthesia	2.19/10,000 (0.02%)
Peripheral nerve blocks	
Interscalene brachial plexus blocks	2.84/100 (2.84%)
Axillary brachial plexus blocks	1.48/100 (1.48%)
Femoral nerve blocks	0.34/100 (0.34%)

What are the risks for the development of neuropathy in neurologically compromised patients undergoing regional block? No study has been able to determine the answer to this question with any degree of certainty. However, predicting the incidence in a nonimpaired patient population may be possible. If the incidence is the minimal likelihood of any given individual developing a neuropathy post–regional block, it is reasonable to consider it the best-case scenario.

In a 2007 publication, Brull and colleagues reviewed 10 years' worth of data from 32 studies that met the inclusion criteria and that were designed to measure neuropathy rates in patients undergoing neuraxial block and PNBs.[12] Although the incidence of perioperative neuropathy was generally 100 times higher after PNBs than after neuraxial blocks, the likelihood of complete resolution without long-term sequelae was much higher after neuropathy induced by PNBs than by central neuraxial blocks (Table 2).[12]

Another question without definitive answers is why certain nerves are susceptible to sustaining a neuropathy following regional anesthesia. Hogan outlined some of the characteristic features of nerves that predispose them to suffering insults that might be long-lasting or permanent.[13] Nerves are not solid unyielding structures, but rather contain a matrix arrangement of a multitude of neural elements that defy ready characterization due to the almost random location of axons in the matrix (Figures 1 and 2). Hogan expressed that the toxicity of injected anesthetic solutions used for regional anesthesia is proportional to the duration of the exposure

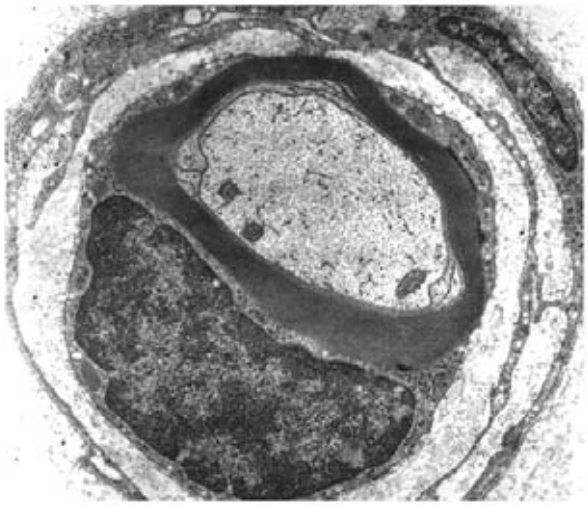

Figure 1. Single myelinated axon.

A single myelinated axon with a perineural sheath.

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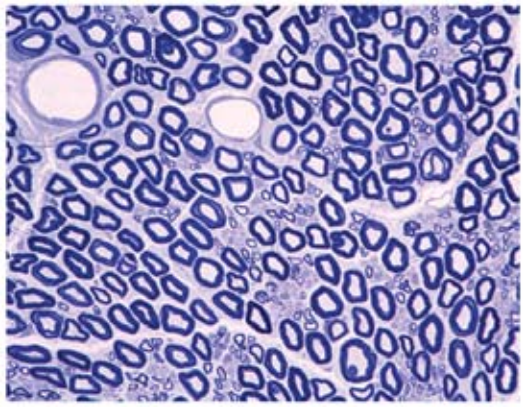

Figure 2. Normal nerve.

Cross section of plastic-embedded normal nerve stained with toluidine blue. Peripheral nerves consist of fascicles that contain myelinated and unmyelinated axons. Myelinated axons (shown as dark rings in this section) vary in thickness.

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of the nerve. In addition, agent-specific alterations in peripheral blood flow can cause ischemic changes in nerves. For example, epinephrine alone produces vasoconstriction, but this does not directly equate with nerve injury. Mechanical effects of nerve blocks, including nerve edema and endoneural herniation may contribute to nerve injury. An ischemic insult to the nerve initially results in depolarization, followed by an increase in spontaneous neural activity. Finally, following less than 2 hours of ischemic time, nerve function typically returns to normal within about 6 hours.[13]

Conditions of Preexisting Neuropathy And Regional Anesthesia

Diabetes Mellitus

Individuals undergoing surgery under regional anesthesia may have subclinical neuropathies (Figures 3 and 4). These patients may be sensitive to the nerve-blocking effects of local anesthetics, and may respond to decreased concentrations of these agents.

The known microangiopathy associated with diabetes may result in an increased exposure of the nerve to local anesthetics. Patients undergoing neuraxial techniques may be at the highest risk for adverse events, according to a retrospective review by Hebl et al of 567 patients with preexisting peripheral sensorimotor neuropathy or diabetic polyneuropathy who underwent neuraxial analgesia or anesthesia at Mayo Clinic in Rochester, MN.[14] Two patients (0.4%) developed a new or progressive deficit following an otherwise uneventful neuraxial block.[14] The incidence of new neuropathy after spinal block (0.3%) was approximately 9 times higher than that noted by Brull and colleagues for neuropathy developing after spinal blocks in noncompromised patients, and approximately 25 times higher for epidural blocks (0.5% vs 0.02%).[12,14]

The rate of neuropathy in diabetics undergoing PNBs remains unknown, but must be considered based on the observations of isolated case reports such as the one by Horlocker et al, in which the same patient undergoing continuous blocks with catheters and infusions developed severe brachial plexopathy on both sides at different settings.[15] However, many questions remain unanswered.[16] These include whether local anesthetics used in standard doses are more toxic in patients with diabetes than in an unaffected population; whether the dose should be different for those with diabetes versus those without the disease; whether the use of a peripheral nerve stimulator for nerve localization is less effective in the diabetic population; and even whether information gleaned from animal studies applies to the human condition of diabetes in making clinical decisions.[16]

Although use of peripheral nerve stimulation (PNS) may be of questionable efficacy for nerve localization in patients with diabetes, some clinicians advocate using ultrasound guidance in these patients as a means of

avoiding PNS. Sites et al were able to perform popliteal sciatic nerve blocks successfully in 2 different patients for whom use of PNS proved unreliable.[17] Evoked motor responses were not forthcoming even with generous stimulating currents of up to 2.4 mA.

Another question is whether the use of continuous techniques predisposes patients with diabetes to persistent neuropathy after surgery. Here, again, the answer must come from retrospective reviews. A review of 405 continuous axillary brachial plexus catheters, including those placed in 40 patients with preexisting neuropathies, found that neither of the 2 new deficits occurred in compromised patients.[18] These results imply that prolonged exposure of impaired nerves to infusions of local anesthetic may not necessarily result in a higher risk for postoperative dysfunction.

Some patients with diabetes likely are predisposed to developing new neuropathies after regional block. However, the incidence, mechanism, and predictability of this phenomenon remain unclear.

Renal Failure

Individuals with renal failure may have neurologic dysfunction, including neuropathies. To date, scant literature has evaluated the relative risks imposed by regional block techniques in these patients with regard to the development of postoperative neuropathy. Case reports form the foundation for understanding this phenomenon, yet also expose the potential for misinterpretation of clinical neuropathy development and attribution to an undeserved cause. For example, Hebl and Horlocker noted the development of neuropathy in a 78-year-old man with chronic renal failure who underwent a transarterial brachial plexus block and who subsequently developed a paretic upper extremity.[19] On evaluation and examination, a diagnosis of ischemic monomelic neuropathy was made, with a brachial artery clot being found during reexplorative surgery, exonerating the renal issue.

Entrapment Neuropathies

Entrapment neuropathies encompass a wide range of seemingly unrelated conditions having a similar outcome; carpal tunnel syndrome, ulnar neuropathy syndrome, and brachial plexopathy all have been implicated in terms of showing susceptibility to the development of neurologic dysfunction after regional block anesthesia. In a retrospective review of 360 patients with ulnar nerve neuropathy undergoing ulnar nerve transposition surgery under general or axillary block anesthesia (72% general; 28% axillary block), 6 block patients developed new-onset neural dysfunction.[20] Each had received bupivacaine as the local anesthetic for the block. Bupivacaine was found to be an independent risk factor for the development of this condition.[20] Note that this 6% incidence of new-onset nerve dysfunction is approximately 4 times greater than that noted in the

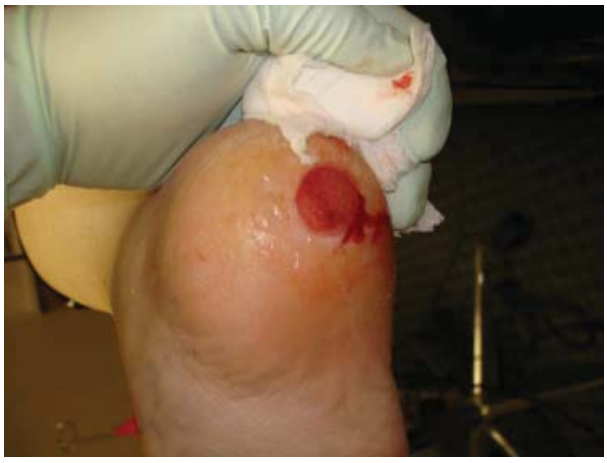

Figure 3. Foot ulcer in a patient with diabetic neuropathy.

Source: *The Foot and Ankle Online Journal*.

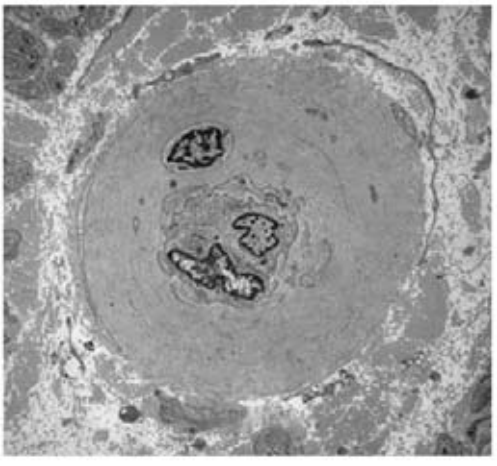

Figure 4. Arteriole in diabetic nerve.

Vascular thickening of an endoneurial arteriole in diabetes.

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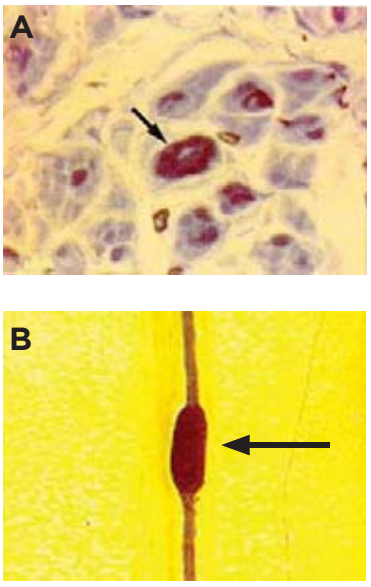

Figure 5. Hereditary neuropathy with liability to pressure palsies.

(A) Note nerve fibers with "thickened" myelin sheath as is seen in semi-thin sections (arrow). In a single teased nerve fiber preparation (B), the "thickened" area appears as a sausage-like structure (tomaculous neuropathy).

Images courtesy of Y. Harati, MD, Baylor College of Medicine.

larger review by Brull et al, for axillary brachial plexus block (6% vs 1.48%).[12] Perhaps the use of axillary brachial plexus techniques is responsible for the difference, although that appears unlikely. A retrospective review of 1,614 axillary blocks performed on 607 patients, including 31% who had multiple blocks within 1 week (2-10 total blocks), found that preexisting neurologic deficits did not increase the risk for neurologic deficits.[21]

Hereditary Conditions

Neuropathies may be acquired or inherited. Among the inherited conditions, several demand scrutiny when evaluating patients as candidates for regional anesthesia. The diagnosis of postoperative neurologic dysfunction typically depends on genetic testing to confirm the existence of an inherited disorder. One such condition is hereditary neuropathy with liability to pressure palsies (HNPP, Figure 5). Genetic testing in such individuals typically demonstrates a 1.5 megabase deletion at chromosome 17p11.2, which bears the peripheral myelin protein-22 (*PMP-22*) gene.[22] HNPP is a rare autosomal dominant condition with variable penetrance, occurring in 16 per 100,000 people in the general population. It is most commonly identified in the second or third decade of life. The hallmark of the condition is painless focal neurologic dysfunction at entrapment sites following minor trauma or compressions. Sausage-shaped swellings of the myelin sheath, called tomacula, also occur. The most commonly affected nerves are the peroneal, ulnar, and radial.[23] Chronic sensorimotor neuropathy or brachial plexus palsy and CNS demyelination may occur in cases of HNPP. These clinical phenomena are believed to result from a *PMP-22* mutation. Recovery from the neuropathy may be slow or incomplete.

The possibility of HNPP should be considered whenever there is development of neuropathy subsequent to a regional block; overlooking this condition may lead to misassignment of blame to the anesthesia care provider. Because this syndrome is not exceedingly rare, it must be part of the differential diagnosis. In obstetrics, for example, with a known incidence of postpartum neurologic deficit occurring in approximately 1% of parturients, the development of a neurologic deficit should still bear the scrutiny of evaluation and investigation to rule out HNPP.[22]

Again, case reports form the basis of our appreciation of the role of this phenomenon in the development of neuropathy after anesthesia and surgery. Even patients with HNPP undergoing surgery under general anesthesia are prone to the development of postoperative neuropathies.[23]

Patients with HNPP also may be prone to the development of schwannomas, although this association is speculative and has been observed only anecdotally.[24] It is tempting, however, to note the association between an abnormal tumor growth of the peripheral nerve and the predisposition to pressure palsies. Further basic research must be conducted to demonstrate a definitive association between these respective abnormalities.

The use of ultrasound guidance for the performance of PNBs may be ideally suited to patients with a documented diagnosis of HNPP. It appears intuitive and inferential that the enlargements (ie, tomacula formation) of peripheral nerves in HNPP may be visualized and thus avoided when advancing needles toward the target nerves, thereby minimizing the potential for traumatic neural injury to occur with the development of neuropathy.[25] Tomaculae may be removed from sites of known entrapment, making their location entirely haphazard and hence prone to injury.

HNPP is increasingly being recognized and reported. As a result, the practitioner of regional anesthesia should consider this diagnosis in patients who lacked obvious risk factors before the performance of a nerve block or central neuraxial technique, but who subsequently present with a postoperative neuropathy.[26-31]

Miscellaneous Conditions

Hereditary conditions (types I, II, and III) are sensorimotor or motor neuropathies that may influence the development of neuropathies following regional

anesthesia (Figure 6). These include 46,XY gonadal dysgenesis; other *PMP-22* gene mutations that are not HNPP; Dejerine-Sottas syndrome (hypertrophic intestinal neuropathy—a rare autosomal recessive disorder associated with demyelination and remyelination–type III); Dandy-Walker syndrome (progressive cystic enlargement of the fourth ventricle); and Charcot-Marie-Tooth (peroneal muscular atrophy), with weakness in the lower extremities and other degenerative joint diseases (Friedreich's ataxia). Each of these conditions may predispose individuals to postoperative neuropathy after either regional block or general anesthesia and should be considered in the differential diagnosis of individuals so presenting.

Charcot-Marie-Tooth has been found to be resistant to the use of PNS guidance for peripheral nerve localization, and as in the patient with diabetes presented above, may be an ideal indication for the use of ultrasound guidance for nerve localization.[32]

Conclusion

No absolute method exists for predicting how the patient with a preexisting neuropathy will fare with a regional block technique. Whether the neuropathy will remain static or become exacerbated is uncertain. Each case must be evaluated individually, and a full appraisal of the risks and benefits associated with and the alternatives to regional anesthesia must be provided to the patient.

The increasing popularity of ultrasound guidance for nerve and plexus localization, allowing the visualization of target structures, might help clinicians to minimize the likelihood of driving needles into neural structures or unintended sites. Documentation of a comprehensive preprocedure evaluation is one of the safest ways to demonstrate that an attempt was made to identify the potential pitfalls in any given situation. Understanding the relative risks for postprocedure neuropathy in a normal population of patients, and advising patients of such risks, is paramount to reducing the likelihood of misunderstanding and the development of resentment in the case of an unexpected, unwanted result. At worst, reliance on retrospective reviews may be a starting point for providing an unfavorable image of regional blocks to patients who insist on full disclosure of how their disease may be influenced by regional anesthesia. In that regard, it is prudent to point out the possibility of a 10-fold increase in the development of new neurologic dysfunction in patients with predisposed, preexisting neuropathy after a neuraxial block,[14] and a 6-fold increase when axillary blocks of the brachial plexus are performed using bupivacaine as the local anesthetic solution.[19] Keeping these contingencies in mind, even these retrospective studies relied on 8 isolated cases to reach these conclusions. In other words, a heavy reliance on these data demands an exceptionally discerning eye.

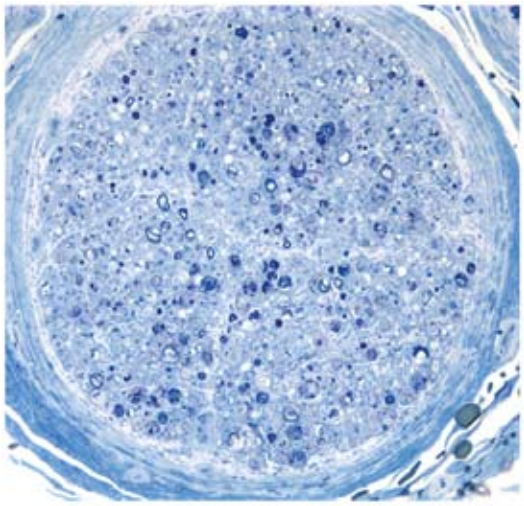

Figure 6. Wallerian degeneration.

Fragmentation and loss of myelin and axons. Cross section of plastic-embedded nerve, toluidine blue stained.

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