J Neuropathol Exp Neurol
Vol. 68, No. 8
August 2009
pp. 833–844

REVIEW ARTICLE

An Update on Nerve Biopsy

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Abstract

Indications for nerve biopsy have decreased during the last 20 years. For the most part, this is a result of progress in the application of molecular biologic diagnostic testing for genetic peripheral neuropathies (PNs) and the increasing use of skin biopsy. The latter is primarily used to evaluate small-fiber PN, although it rarely discloses the specific etiology of a PN. Nerve biopsies are usually performed on either the sural or the superficial peroneal nerve, the latter in combination with removal of portions of the peroneus brevis muscle. The definite diagnosis of vasculitic lesions can be readily established on small paraffin-embedded nerve biopsy samples, although in some cases, the characteristic lesions are only apparent in muscle specimens. Other nerve specimens are routinely fixed in buffered glutaraldehyde and prepared for semithin sections and electron microscopy; frozen specimens are used for immunofluorescence studies. Electron microscopy is of great value in some cases of chronic inflammatory demyelinating polyneuropathies, monoclonal gammopathy, and storage diseases. Because more than 30 genes may be involved in genetic PNs, analysis of nerve lesions can direct the search for mutations in specific genes. Electron microscopy immunocytochemistry is mandatory in some cases of monoclonal dysglobulinemia. Thus, nerve biopsy is still of value in specific circumstances when it is performed by trained physicians and examined in a laboratory with expertise in nerve pathology.

Key Words: Electron microscopy, Myelin, Nerve biopsy, Peripheral neuropathy.

INTRODUCTION

Diagnostic nerve biopsies (NBs) have been performed since the end of the 1950s (1–3); the advent of electron microscopy (EM) provided a new impetus (4, 5). There is now debate regarding the usefulness of NBs, and indications have declined for 2 main reasons, that is, progress in diagnostic molecular biology and the loss of technical expertise; there are fewer and fewer laboratories with the expertise necessary for detailed study of human NB. Only a few patients diagnosed as having a polyneuropathy need an NB, and experienced neuropathologists must clearly communicate to clinicians the various morphological methods that can be used and how to use them. Nerve biopsy specimens should be analyzed only in specialized laboratories (www.unilim.fr/neurolim) (6–13).

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NERVE BIOPSY METHODS

Because NB is an invasive procedure, patients need to be selected based on strict criteria; the absence of cutaneous lesions and normal coagulation tests are required (11, 13). Any sensory nerve can be biopsied, but the sural nerve is the most commonly chosen because of its well-known topography (11). The superficial peroneal nerve is frequently biopsied in France because fragments from the adjacent peroneus brevis muscle can be readily taken from the same incision; a few other groups have adopted this method (14). Irrespective of the nerve chosen, a whole segment of nerve is usually taken (15).

The nerve and muscle specimens must be carefully prepared immediately after removal using all of the following techniques: the nerve fragment is divided into 3 specimens. The first is put into buffered formalin and then embedded in paraffin. The second is put into buffered glutaraldehyde for 1 hour and then postfixed and embedded in a resin such as Epon or LR white to prepare semithin and ultrathin sections and for subsequent immunoelectron microscopic examination. Teased fibers may also be prepared. The third specimen is frozen for immunofluorescence study. Nerve samples can be sent by mail to specialized laboratories. Because it is difficult to send frozen samples, immunoelectron microscopy studies can be carried out instead of immunofluorescence. If a neuromuscular biopsy has been done, several muscle fragments are also prepared in the same way.

Skin biopsy has proven to be useful to confirm and quantify fiber loss in small-fiber peripheral neuropathies (PNs), but the limitations of skin biopsy have been pointed out by several authors (16, 17).

Complications of NBs are rare. Only a few studies have attempted to determine the type and incidence of complications. Dyck et al (11) reported that approximately 60% of patients had no symptoms after sural NB, whereas 30% experienced some subjective and objective sensory abnormalities that resolved with time (11, 12).

HISTOPATHOLOGIC STUDIES

Elementary Lesions

Basic findings are first determined by microscopic examination of paraffin-embedded fragments; myelinated fibers are first analyzed on semithin sections and then by

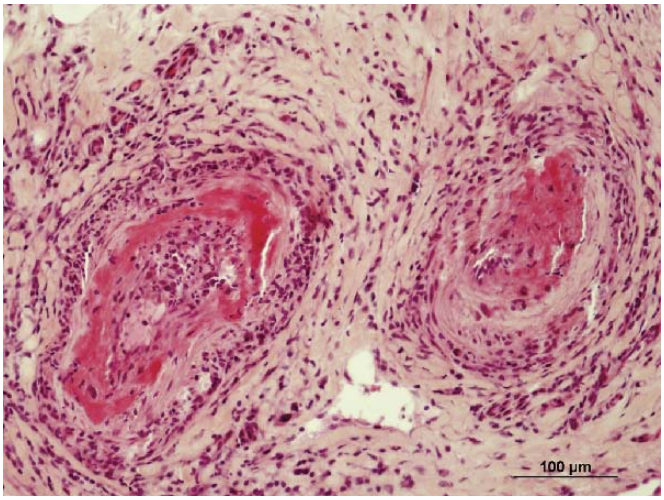

FIGURE 1. Hematoxylin and eosin-stained transverse paraffin section of a nerve biopsy in a case of polyarteritis nodosa. There are 2 markedly inflamed vessels with fibrinoid necrosis in the epineurium.

EM. The latter are usually conducted on cross sections, but examination of longitudinal sections of myelinated and unmyelinated fibers may be necessary to study specific structures such as nodes of Ranvier and intra-axonal mitochondria.

Acute axonal degeneration is characterized by the presence of numerous ovoids containing axonal and myelin debris that can also be seen clearly on nerve teasing and EM. In cases of chronic axonal involvement, there is a more or less severe fiber loss, sometimes followed by the development of clusters of 3 or 4 regenerating axons, some of which are remyelinating. Progressive axonal loss is a consistent feature in the course of any type of chronic polyneuropathy, but in severe and chronic forms of acquired or hereditary polyneuropathy, demyelinating lesions that contributed to the marked axonal loss may be masked. A significant loss of large myelinated fibers can account for abnormal electrophysiological findings; by contrast, the loss of small myelinated fibers and unmyelinated fibers without significant decrease of large myelinated fibers will be only detected by examination of semithin sections and EM.

Demyelination is characterized by the presence of some fibers, the myelin sheaths of which have disappeared or are regenerating, as indicated by their thinness relative to the diameter of the axon. This is sometimes associated with *tomaculae*, myelin outfoldings or giant axons, all of which can be observed on teased fibers. Nerve fiber teasing is, however, rather time consuming, and such features are better observed by EM. Macrophage-associated demyelination is confirmed when the cytoplasm of a Schwann cell is invaded by a histiocyte, the elongated processes of which dissociate and destroy myelin lamellae, leaving the axon with a normal or only slightly modified appearance. Such a lesion may be suggested in semithin sections, but the integrity of the axon and the intramyelinic cytoplasmic processes can only be ascertained by EM (4–11, 13, 18, 19). Several types of artifacts must be recognized to avoid misinterpretation (12, 13).

NB May Be the Only Way of Determining the Etiology of Certain Neuropathies

Vasculitic Neuropathy

Most patients with vasculitic neuropathy have a primary systemic vasculitis (Fig. 1), and they clinically present with a multiplex mononeuropathy. Nerve biopsy can establish that the vasculitis is responsible for this disorder and, thus, instigate prompt treatment (20). Confirmation of the characteristic arteriolar lesions is based on a modified version of the international classification established by Jennette et al (21) in 1994 that is suitable for nerve pathology (14, 22). In some cases, necrotizing vasculitis corresponds to the classic periarteritis nodosa in which medium-sized arterioles, but not small arterioles, are involved; some of these patients may be infected with hepatitis B virus. Most cases of necrotizing vasculitis correspond to microscopic polyangiitis, which involves small and sometimes medium-sized arterioles (Fig. 1) (21). In a recent series, there were 56 cases of microscopic polyangiitis among 60 cases with necrotizing vasculitis (22). The characteristic lesion of necrotizing vasculitis on neuromuscular biopsies is fibrinoid necrosis (Fig. 2), which destroys the media with fragmentation of the internal elastic lamina; inflammatory cells, mainly lymphocytes and histiocytes, are visible in the external part of the arteriole. Polymorphonuclear leukocytes are numerous in the early stage, but eosinophils are rare and scattered at every stage of this classic form. Sometimes fibrinoid necrosis is only visible in small areas of the media or is occasionally seen as homogeneous dark areas on EM (Fig. 2). In older lesions, extensive fibrosis replaces fibrinoid necrosis, but inflammatory cells are still visible at the periphery. Arteriolar lesions at different stages can be observed in both muscle and nerve or in isolated muscle or nerve specimens. In this series of 60 cases with typical lesions of necrotizing

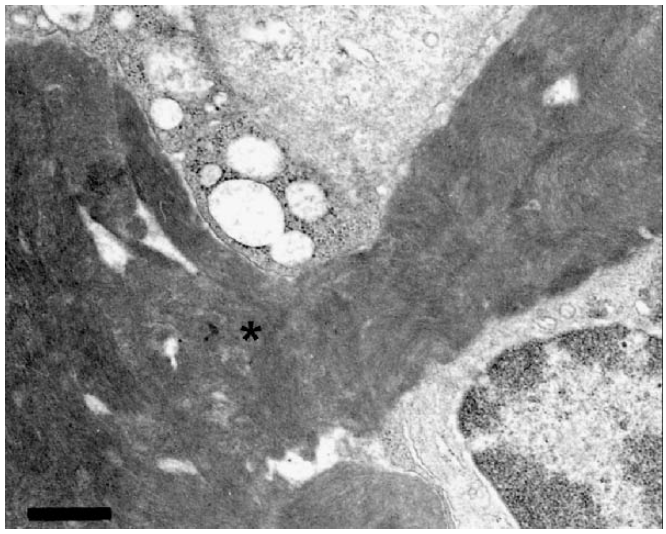

FIGURE 2. Electron microscopy in a case of microscopic polyangiitis. The dark and amorphous deposit (asterisk) corresponds to an area of fibrinoid necrosis in the media of an arteriole. Scale bar = 1 µm.

vasculitis, such lesions were only visible in muscle specimens in 31% of cases.

Microvasculitis is one of the terms describing vasculitis involving small vessels, in the absence of necrosis, with T lymphocytes and histiocytes infiltrating the thin vessel walls (21). This has also been called *lymphocytic vasculitis* (7) and should not be confused with *perivascular inflammatory infiltrates*, in which vessel walls are not involved (23). Such inflammatory infiltrates are not diagnostic if they remain isolated, but they indicate a probable vasculitis when they are associated with at least one of the following alterations: 1) neovessels visible in the epineurium; 2) numerous red blood cells in the vicinity of nerve fibers and corresponding to an endoneurial purpura; 3) asymmetric fiber loss and/or asymmetric distribution of ovoids in the same fascicle or between 2 adjacent fascicles (14, 22, 24); or 4) giant axons packed with organelles and surrounded or not by a thin myelin sheath are also significant. In a large series, 24 patients had nerve lesions indicative of vasculitis (22).

Nonsystemic vasculitis restricted to the sural nerve was noted by Dyck et al (24) in 1987 and later by other authors, but adjacent muscle vessels are also involved by the inflammatory process (14, 22). Another report has confirmed the better prognosis of such localized vasculitis (25). In most cases of vasculitic PN, the nerve fiber lesions were essentially axonal with fiber loss and/or acute axonal degeneration (14, 22, 24).

Churg-Strauss syndrome is a distinct clinical entity in which systemic vasculitis is associated with hypereosinophilia (>10%) and adult-onset asthma. Because peripheral nerve involvement sometimes dominates the clinical picture, the NB may disclose lesions of necrotizing vasculitis associated with eosinophil infiltrates. In a series of 24 cases, characteristic lesions were found in 15 patients and solely in the muscle specimens in 8 patients (26).

Vasculitic neuropathy is sometimes associated with another connective tissue disease of which rheumatoid arthritis is probably the most common (27, 14). Cryoglobulinemic neuropathy is sometimes associated with necrotizing vasculitis, particularly when there is a hepatitis C virus infection (28), and rarely with microvasculitis. The seminal description of the entity by Jennette et al (21) did not mention peripheral nerve involvement. On the other hand, Wegener granulomatosis is rarely associated with genuine vasculitic neuropathy; it was seen in 2 of 70 patients by Collins et al (14) and only 2 probable vasculitis in 178 patients in another study (19). The association of vasculitis with sarcoid nerve lesions has been demonstrated in several cases (29, 30).

Sarcoid Neuropathy

Nerve biopsies have been examined in 38 well-documented cases of sarcoid PN (31). Overall, sarcoid PN corresponded to 17 cases of chronic sensorimotor PN, 14 cases of mononeuropathy multiplex, 3 cases of painful PN, and 5 cases of chronic inflammatory demyelinating polyneuropathy (CIDP). Characteristic noncaseating granulomas (NCGs) were observed in the NP sample (mostly in the epineurium) or in muscle alone, and they were also detected in lung or lymph node specimens. Muscle biopsy specimens had well-developed NCG with larger multinucleated giant cells. Noncaseating granuloma in muscle specimens rules out the diagnosis of tuberculoid leprosy because muscle tissue is not involved in that condition (30). Interestingly, sarcoidosis was apparently restricted to muscle and nerve in 6 cases in the literature, emphasizing the importance of nerve and muscle biopsy (31). Most sarcoid PNs are characterized by axonal degeneration with loss of myelinated fibers or the presence of numerous ovoids in acute cases. In a few cases, however, primary demyelinating lesions were also observed (30–32). Nerve fiber degeneration has been linked to compression by endoneurial granulomas or to vascular deficiency; both mechanisms may be incriminated in some cases (29–31).

Neuropathies Associated With Infection

Lyme Disease

Subacute meningoradiculoneuritis with facial palsy and distal involvement of the peripheral nervous system (PNS) is encountered in 15% to 20% of patients with Lyme disease. Nerve biopsy shows inflammatory infiltrates with lymphocytes and plasma cells mainly around small vessels in the epineurium and endoneurium; the lesions of nerve fibers are acute and axonal (33, 34).

Human Immunodeficiency Virus Infection

Neuropathies in human immunodeficiency virus infection are usually classified according to the stage of the infection (35). Inflammatory demyelinating PN occurs mainly during the early stage of human immunodeficiency virus infection either in the form of Guillain-Barré syndrome or CIDP; characteristic macrophage-associated demyelination is observed by EM in some cases (36). Multiplex mononeuropathies are mainly caused by necrotizing vasculitis and have been mentioned in studies of vasculitic neuropathy (22, 37). Sensory PNs are mainly axonal and considered to be length dependent. The antiretroviral toxic PN has the same clinical and histological features. Among the opportunistic infections, cytomegalovirus, which causes a polyradiculoneuropathy in roots of the cauda equina and in lumbar segments, is probably the most common (38).

Leprous Neuropathy

Leprous neuropathy may be encountered in the western world in migrants from endemic areas. Histological diagnosis is necessary and can be suggested in cutaneous lesions in some cases, but NB is often required (5–7, 39), or it can reveal this diagnosis in an apparently idiopathic PN. In lepromatous neuropathy, nerve fascicles are infiltrated by "foamy" cells, corresponding to macrophages that contain elongated globi with accumulation of typical bacilli. These are visible by Ziehl staining or on EM in the epineurium, perineurium, and endoneurium. Bacilli are also seen in Schwann cell cytoplasm by EM as rod-shaped structures located in a round clear halo. Tuberculoid leprosy is characterized by granulomas containing numerous histiocytes and a few multinuclear giant cells. Caseation necrosis is sometimes visible in such granulomas. Bacilli are very rare in tuberculoid lesions; sarcoidosis can be ruled out if large muscle fragments are not involved.

Inflammatory Demyelinating Polyneuropathy

Nerve biopsy is not indicated in the classic forms of Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy), although it may be recommended in rare fulminant cases. In such instances, there is a widespread acute degeneration of myelinated fibers; it is of interest that some of these cases were initially considered as locked-in syndrome (C. Vital, unpublished data).

In a retrospective series, we found that 8 of 44 consecutive patients had pathological findings indicative of CIDP but did not meet any of the usually accepted electrophysiological criteria for this diagnosis. Among these 8 patients, 6 were treated, and 5 responded favorably to treatment. These 8 patients had an electrophysiological pattern of axonal neuropathy with subtle additional signs of demyelination that prompted us to perform an NB (40). The histopathologic diagnostic criteria of the American Academy of Neurology for CIDP require the detection of more than 5 demyelinated fibers (41). In some cases, the heterogeneous distribution of these demyelinating and remyelinating lesions between different fascicles and inside some fascicles may be apparent on semithin sections at low magnification. Various extents of onion bulb proliferations of concentric Schwann cell processes are seen around more or less completely demyelinated axons. In some cases, such axons may be devoid of myelin sheath or wrapped only by a few myelin lamellae, indicating a remyelinating process. The shape, size, and internal structure of these axons are usually only slightly modified. A few perivascular T cells may be seen in paraffin-embedded or frozen sections, and a few macrophages may be scattered in the endoneurium (19). By EM, macrophages may be seen to have destroyed the myelin sheath (Figs. 3, 4). Myelin debris is also occasionally seen within macrophages well removed from the Schwann cell cytoplasm, and axonal loss is a consistent finding. These secondary axonal changes develop at variable rates; in almost all cases, there are clusters of regeneration that reflect abortive attempts at repair. Such lesions are also seen in cases of CIDP associated with a monoclonal dysglobulinemia or any other general disorder.

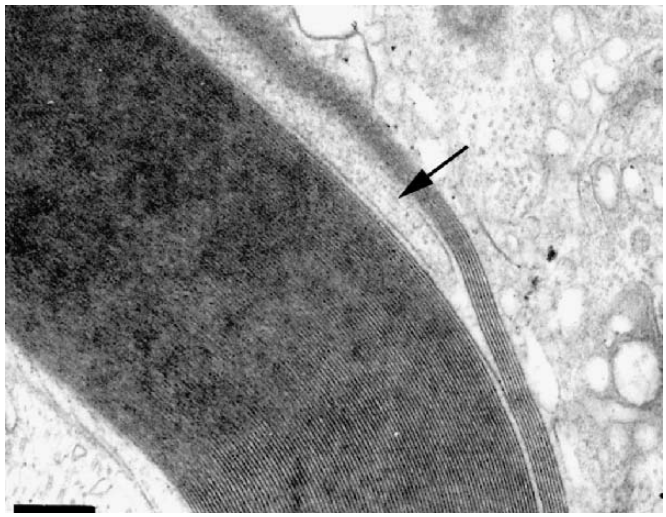

FIGURE 3. Electron microscopy of a nerve biopsy in a case of chronic inflammatory demyelinating polyneuropathy. The external portion of the myelin sheath is dissociated by the elongated process of an invading histiocyte (arrow). Transverse section. Scale bar = 500 nm.

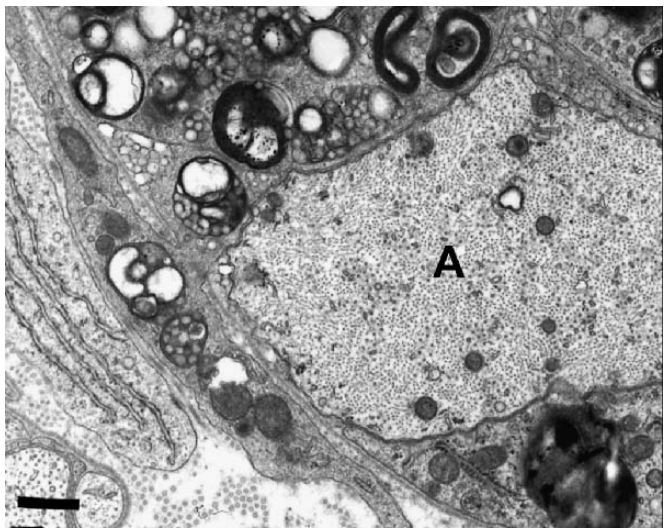

FIGURE 4. Electron microscopy in a case of chronic inflammatory demyelinating polyneuropathy. A histiocyte (partly located in the endoneurium) has invaded the Schwann cell cytoplasm and has destroyed the myelin sheath. The axon (A) seems unaltered. Transverse section. Scale bar = 1 μm.

Nerve biopsy should be considered on a case-by-case basis but should be reserved for clinically and/or electrophysiologically atypical cases. Without the NB findings, a significant number of unrecognized CIDP patients may be classified as having chronic idiopathic axonal neuropathy and may not be treated appropriately. In cases in which nerves are electrophysiologically unexcitable, a variety of demyelinating lesions is observed. The place of NB in clinical management has been recently discussed elsewhere (42).

Polyneuropathy Associated With Monoclonal Gammopathy

Because various types of PN may be observed in any type of benign or malignant monoclonal gammopathy (MG), a coincidental association needs to be ruled out and the link between the PN and MG needs to be demonstrated (43). In particular, NB may be of importance in patients treated with potential neurotoxins. Unfortunately, clinical and electrophysiological data cannot discriminate between a PN induced by a therapeutic agent and other mechanisms. On the other hand, aggressive treatments such as chemotherapy and bone marrow transplantation may be indicated if the NB demonstrates that the nerve lesions are a direct consequence of the hematologic disorder. The incidence of these lesions is probably underestimated.

Endoneurial Immunoglobulin Deposits Within Myelin Sheaths

IgM. In cases of PN with serum anti-MAG antibodies, the clinical, electrophysiological, and biochemical findings usually obviate NB. Nevertheless, the characteristic widening of

myelin lamellae can sometimes be observed by careful EM of an NB several years before the monoclonal MG is evident in the serum (44). Some exceptional associations such as amyloid deposits may also only be proven by NB. A biclonal gammopathy, IgM-kappa with antimyelin activity and an IgG-lambda chain linked to amyloid deposits, was observed in one of our patients (45). Otherwise, some patients may have anti-MAG IgM activity in their serum and lymphoma cells (44) or IgM endoneurial deposits in their nerve interstitial tissue (46). Immunohistochemical study of the cells and deposits is required to identify the incriminated immunoglobulin.

IgG, IgA. In patients with monoclonal IgG or IgA, the antigens are unknown and there is no anti-MAG activity. In rare cases, direct immunofluorescence with specific anti-immunoglobulin antibodies demonstrates annular binding to many myelinated fibers. By EM, numerous foci of widening of the myelin lamellae comparable to that found in IgM anti-MAG PN are observed (Figs. 5, 6). We have noted that these lesions may sometimes be associated with other specific anomalies such as abnormal immunoglobulin deposits in the endoneurial interstitial tissue. Such findings argue in favor of the circulating MG causing the PN (47, 48). In some rare cases of IgA MG of unknown significance (MGUS), globulin deposits are visible as crystalline inclusions either in the Schwann cytoplasm or in the endoneurium (49). Such deposits have also been described by Schroëder (9), but the type of immunoglobulin was not indicated.

Endoneurial Immunoglobulin Deposits in Interstitial Tissue

Immunoglobulins. Although they may be difficult to identify because they are usually scarce, other types of endoneurial immunoglobulin deposits can only be detected by NB. These lesions are not to be confused with amyloid deposits on routine staining and are better identified by immunocytochemistry on frozen sections and EM (5, 46). Depending on their size, they can be detected either by immunofluorescence on frozen sections or, if very small, by EM in which they tend to have a distinctive aspect as digitiform, fibrillar, or tubular structures. Otherwise, immunoelectron microscopy using anti-immunoglobulin antibodies is required to confirm the immunoglobulin specificity of such deposits. In any case, a cryoprotein should be sought and, if present, should be extracted from the patient's blood and fixed; the ultrastructure of the serum protein can then be compared with that of the endoneurial deposits (50). In rare cases of IgA MG, crystalline inclusions may be observed in the endoneurium (Fig. 7) (49).

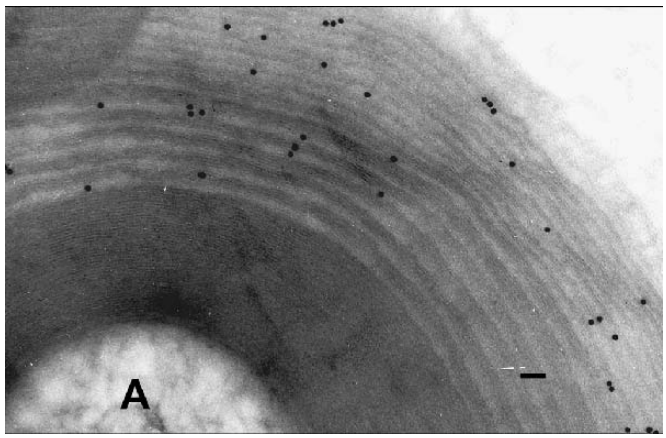

FIGURE 6. Immunoelectron micrograph in a case of monoclonal IgA monoclonal gammopathy of unknown significance and neuropathy. Immunolabeled IgA gold particles are present in the areas of widening of the myelin lamellae. A, axon. Scale bar = 0.1 μm.

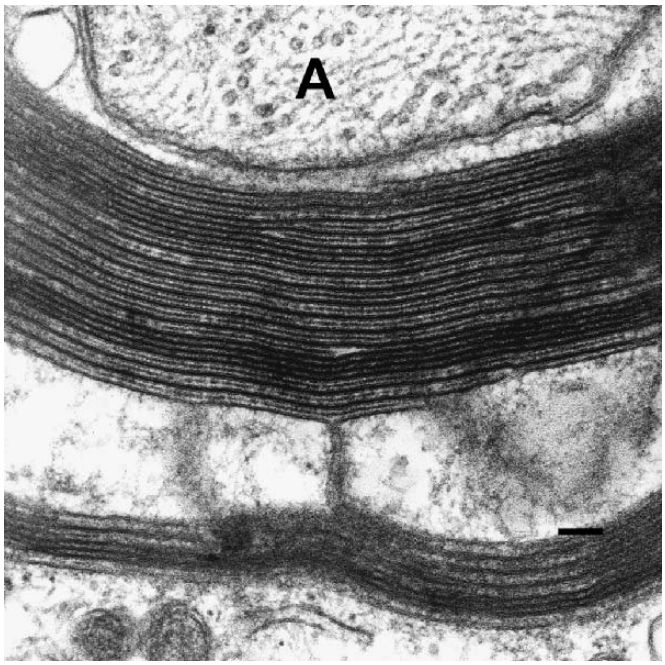

FIGURE 5. Electron microscopy in a case of monoclonal IgG myeloma and neuropathy. There are numerous foci of widening of the myelin lamellae. The intraperiod lines are intact. A, axon. Scale bar = 0.2 μm.

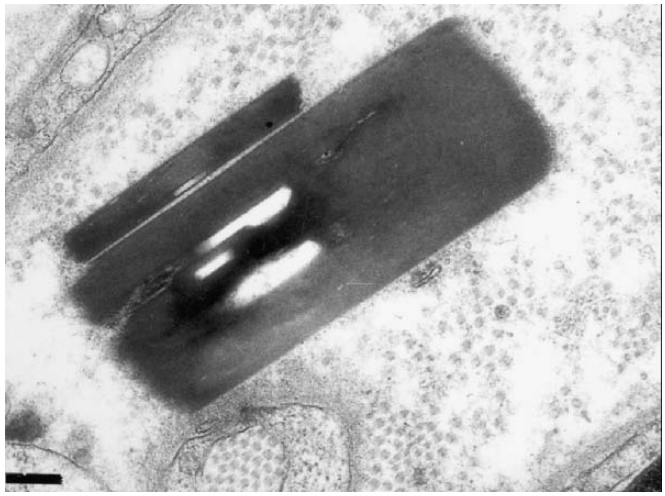

FIGURE 7. Electron microscopy of a transverse section of nerve in a case of IgA gammopathy of unknown significance and neuropathy. There are 2 rectangular crystalline inclusions in the endoneurium. Scale bar = 500 nm.

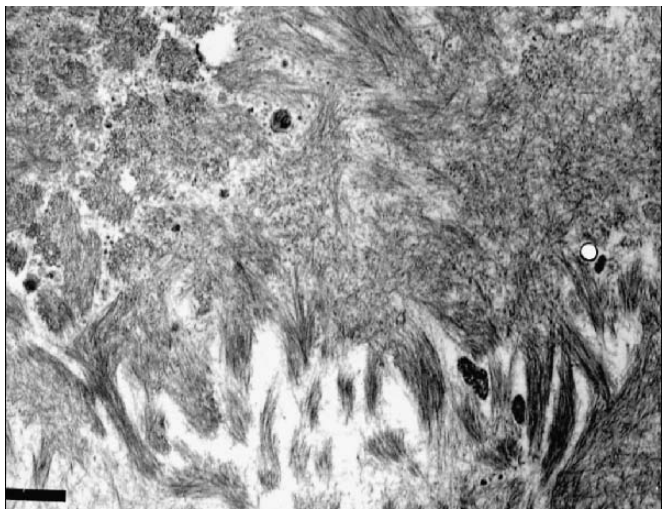

FIGURE 8. Electron microscopy in a case of amyloid neuropathy. Bundles of amyloid filaments are visible in the endoneurium. Scale bar = 1 μm.

Amyloid. Amyloid deposits result from the transformation of an immunoglobulin light chain. The sensitivity of NB for the diagnosis of systemic amyloidosis is 85% (51). In most cases, amyloid deposits are clearly visible on paraffin-embedded sections in the form of round deposits scattered in the endoneurium and sometimes joined to thickened capillary walls (52). Sometimes the deposits are very small, and their amyloid nature can be ascertained by Congo red and thioflavin staining in paraffin sections. Because amyloid deposits can vary greatly among different fascicles, every fascicle or several blocks should be scrutinized. Light chains should be identified on frozen specimens with a specific antibody because immunohistochemical study on paraffin sections can be misleading. Electron microscopy will establish the diagnosis in most cases; sometimes deposits not seen on light microscopic examination will be detected. Amyloid deposits are extracellular and composed of characteristic bundles of unbranched 7- to 10-nm-wide fibrils in an irregular matted form (Fig. 8) and are sometimes seen in intimate contact with endothelial cell basement membranes, Schwann cells, and collagen. Electron microscopy also helps differentiate the bundles of straight filaments from granular deposits of light-chain origin (48). The myelinated fibers may be thinned out in a diffuse pattern or there may be loss of both large and small myelinated fibers (52). The severity of the lesions is suggestive of amyloid PN, whether of genetic origin or amyloid light-chain type. In an apparently amyloid light-chain PN, molecular genetic study sometimes discloses a transthyretin (TTR) mutation, the genuine cause of the amyloidosis (53, 54). Immunoelectron microscopy is of value for differentiating amyloid deposits because of light chain from TTR.

Intraneural Malignant Cells

The presence of lymphoma B or T cells in the nerve parenchyma, usually in the epineurium, can only be shown by NB and confirmed by immunopathologic examination. It may be a known lymphoma or leukemia, or the PN may be a presenting feature (5, 55, 56); sometimes it relates to an MG (43, 57). In such cases, the NB may also help determine whether the PN is caused by the abnormal immunoglobulin or the presence of the lymphoma cells or to both. A negative NB does not rule out a lymphomatous intraneural proliferation because the distribution of the malignant cells is usually patchy. In rare cases, cells of an intravascular large-cell lymphoma are observed in vascular lumens in nerve and muscle specimens (58).

Polyneuropathy, Organomegaly, Endocrinopathy, MG, and Skin Changes Syndrome

In this syndrome, specific immunocytochemical study of myelinated fibers and of the endoneurium is negative, but EM may disclose the characteristic features of this condition, uncompacted myelin lamellae, which may be seen in 1% to 7% of the myelinated fibers in 80% of cases (Fig. 9) (59). This myelin modification corresponds to portions of the mesaxon that are neither flattened nor compacted and that are visible at least around 1 semicircumference of the axon on 3 or more consecutive lamellae. These lesions must be differentiated from the widened myelin lamellae observed in patients with IgM anti-MAG positivity. Thus, the presence of numerous uncompacted myelin lamellae may help distinguish POEMS from CIDP and other demyelinating peripheral nerve disorders, primarily in the early phase.

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy in association with an MG (often IgG) is well recognized. This type of PN may be the result of a common immunologic disorder, the primary target antigen of which remains unknown. As for the classic CIDP cases, NB has no value in typical cases but may be useful in diagnosing atypical ones. The histological lesions are the same as those previously described on CIDP.

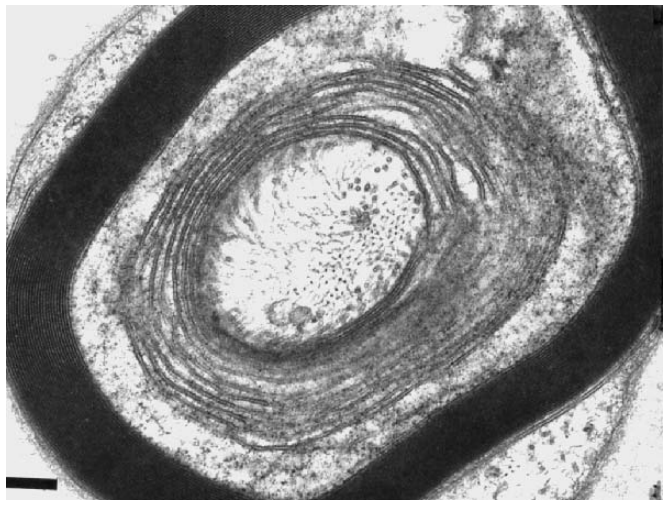

FIGURE 9. Electron microscopy of nerve in polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome. The inner part of this myelin sheath is not compacted. Transverse section. Scale bar = 500 nm.

TABLE 1. Histologic Features That Suggest Specific Genetic Abnormalities in Charcot-Marie-Tooth Diseases

Genes That May Be Affected	CMT Diseases	Abnormal Microscopic and Ultrastructural Features
PMP22 duplication, mutation	AD-CMT 1A	Onion bulbs
PMP22 deletion	AD-HNPP	Tomaculae
P0 mutations	AD-CMT 1B	Uncompacted myelin, onion bulbs, myelin outfoldings
EGR2, P0	CHN	Very severe demyelination, dysmyelination, or no myelin
Cx 32	AD-CMTX	Clusters of regeneration
MTMR 2, 13, Fragmin	AR-CMT 4B, 4H	Myelin outfoldings
KIAA 1985	AR-CMT 4C	Basal proliferation (onion bulbs), unmyelinated fiber involvement
Periaxin	AR-CMT 4F	Abnormal paranodal loops
NF-L	AD-CMT 2E and 1F	Giant axons
MFN2, GDAP1	AD-CMT2	Mitochondrial anomalies
Lamin	AR-CMT2	Severe rarefaction of large myelinated fibers without regenerating clusters

AD, autosomal dominant; AR, autosomal recessive; CHN, congenital hypomyelinating neuropathy; CMT, Charcot-Marie-Tooth; CMTX, Charcot-Marie-Tooth X-linked dominant; HNPP, hereditary neuropathy with liability to pressure palsies.

Hereditary Neuropathies

Charcot-Marie-Tooth Diseases

Recent advances in molecular genetics have substantially modified the approach to Charcot-Marie-Tooth (CMT) disease and related PN. In many cases, the mode of inheritance along with the clinical and electrophysiological data may be sufficient to identify the causative mutations. Nevertheless, at the present time, rapid screening of about 25 causative genes is not feasible for a single patient, particularly if the case is sporadic. It is costly and can only be carried out by highly specialized laboratories. Until the advent of more automated methods of genotyping, detailed histological analysis of the nerve lesions can direct the search for mutations in specific genes (Table 1). For example, *PMP22* duplication or mutations and *MPZ* mutations usually induce numerous large onion bulb formations (60); they consist of Schwann cell processes and more rarely of basal membranes (often encountered in *EGR2* [*Krox20*] mutations) or both, encircling axons with abnormally thin or relatively thick myelin sheaths. These lesions of demyelination and remyelination are not specific for CMT-1. In some *MPZ* mutations, EM will also detect characteristic anomalies of myelin compaction; such aspects are quite specific because MPZ is one of the proteins involved in myelin compaction (Fig. 10). *GJB1* mutations may be suggested by the presence of prominent clusters of regenerating thinly myelinated fibers with scattered onion bulbs and unusually frequent alterations of paranodal myelin (61). *MTMR2*, *MTMR13*, *FGD4*, and *MPZ* mutations are often responsible for numerous outfoldings of myelin (Fig. 11). In some NB of patients with *MPZ* mutations, there may also be anomalies of myelin compaction and outfoldings (62). These outfoldings are different from typical tomaculae formations characterized by focal hypermyelination with smooth external contours. Such tomaculae have been described in hereditary neuropathy with liability to pressure palsy, a disease caused by a deletion of *PMP22*. Ultrastructural anomalies of axonal mitochondria, which are easier to see on longitudinal sections, may suggest *MFN2* (Fig. 12) (63) and ganglioside-induced differentiation-associated protein 1 (GDAP1) mutations; a significant number of mitochondria seem smaller than normal, spherical instead of tubular, and focally accumulated. Otherwise, *KIAA 1986* gene mutations induce thin Schwann processes connecting isolated unmyelinated axons and as supernumerary extensions. *PRX* mutations give rise to subtle anomalies of the nodes of Ranvier; *LMNA* mutations give rise to a severe loss of myelinated fibers with no evidence of regeneration (64). In a few cases of *PMP22* duplication (65) and GDAP1 mutation, inflammatory cells have been observed, suggesting a pathogenetic role of the immune system.

Hereditary Sensory Autonomic Neuropathy

Only EM can detect isolated involvement of unmyelinated axons in this condition (Fig. 13).

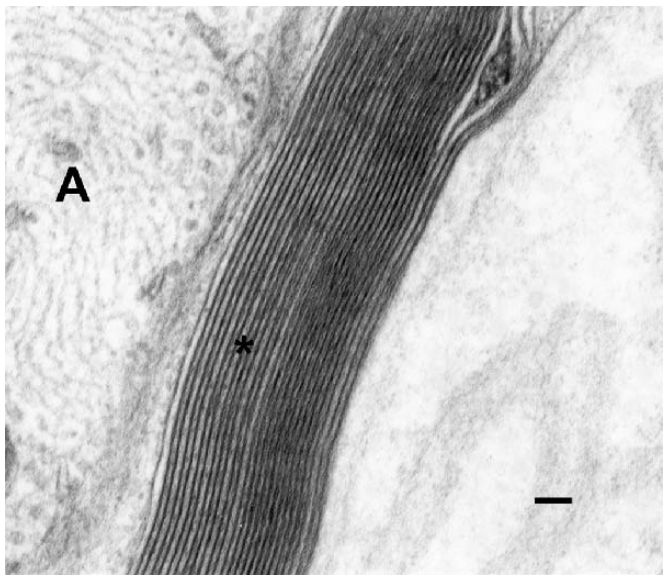

FIGURE 10. Electron microscopy of a transverse section of nerve in Charcot-Marie-Tooth Type 1B demonstrates regular uncompacted lamellae of the myelin (asterisk). A, axon. Scale bar = 0.1 μm.

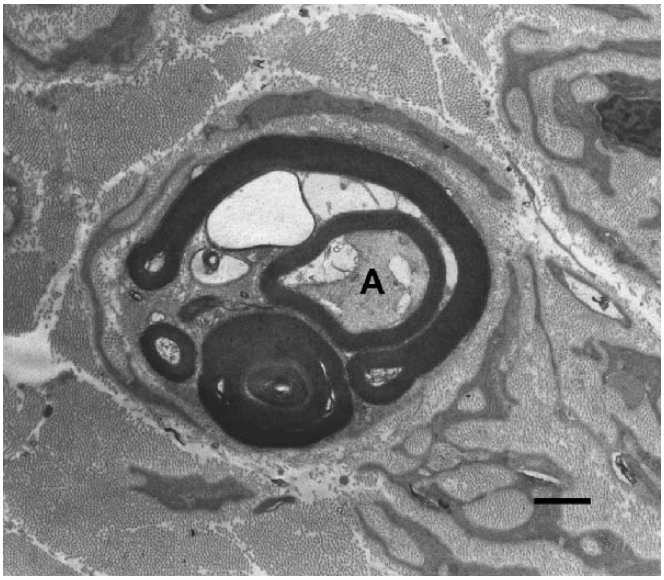

FIGURE 11. Electron microscopy of a transverse section of nerve in Charcot-Marie-Tooth Type 4B1 demonstrates numerous myelin outfoldings of this myelin sheath. A, axon. Scale bar = 2 μm.

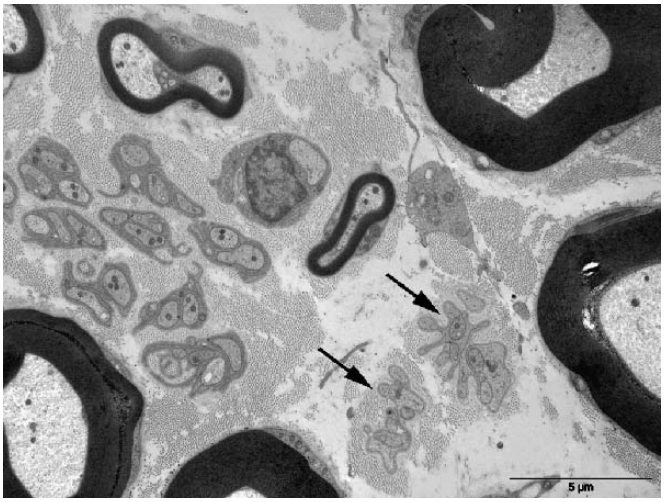

FIGURE 13. Electron microscopy of a transverse section of nerve in hereditary sensory and autonomic neuropathy demonstrates isolated involvement of unmyelinated axons (arrows).

Familial Amyloid Neuropathy

Familial amyloid neuropathy is usually diagnosed by demonstrating a mutation in the *TTR* gene by molecular genetic methods, but the condition can be diagnosed by NB in apparently idiopathic cases. The light microscopic and EM findings are the same as those described for amyloid light chain, except for TTR immunolabeling of the amyloid deposits.

Giant Axonal Neuropathy

Giant axonal neuropathy is a severe autosomal recessive childhood disorder that affects both the PNS and the CNS and is caused by mutations of gigaxonin. Most giant axonal neuropathy patients have the classical clinical phenotype characterized by a severe axonal PN with kinky hair and early-onset signs of CNS involvement. Nevertheless, other phenotypes are possible, such as CMT or spastic paraparesis. Nerve biopsy reveals the diagnosis by showing the giant axons dilated by an intense proliferation of neurofilaments (Fig. 14).

Infantile and Juvenile Neuroaxonal Dystrophy (Seitelberger Disease)

In infants, there is involvement of the CNS where spheroid bodies are seen. Nerve biopsy may detect focal axonal swellings in myelinated and unmyelinated axons.

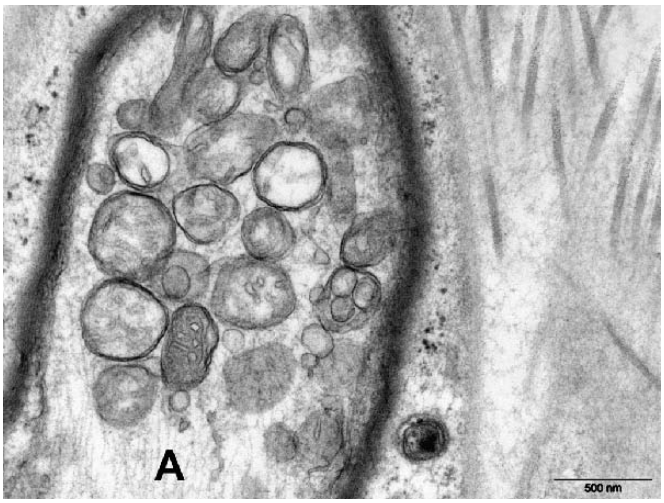

FIGURE 12. Electron microscopy of a longitudinal section of nerve in Charcot-Marie-Tooth Type 2A2 demonstrates abnormally aggregated small round mitochondria in this axon (A) with disruptions of crystae.

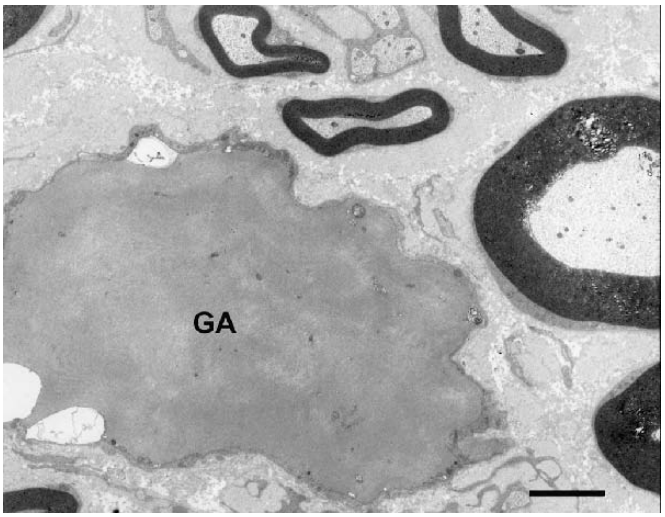

FIGURE 14. Electron microscopy of a transverse section of nerve in giant axonal neuropathy. A giant axon (GA) is dilated by an intense proliferation of neurofilaments. Scale bar = 5 μm.

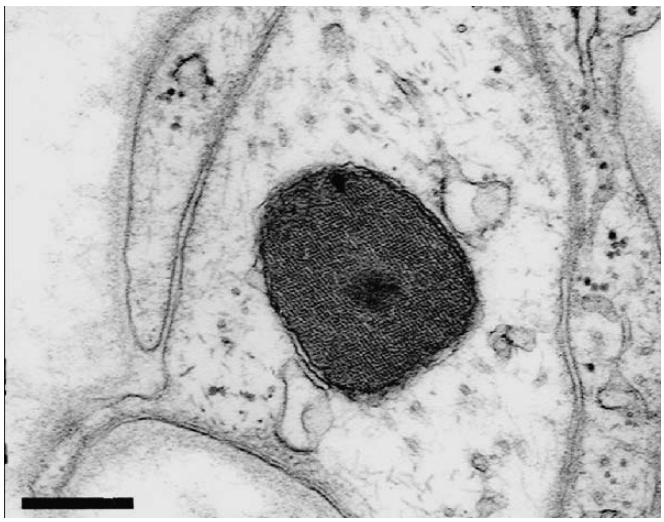

FIGURE 15. Electron microscopy of a transverse section of nerve in idiopathic polyneuropathy. A Fardeau-Engel body with its paracrystalline-like ultrastructure is visible in the cytoplasm of an unmyelinated fiber. Scale bar = 500 nm.

They correspond to disorganized proliferations of vesicles or tubules of 20- to 40-nm diameter.

Mitochondriopathies

The classification of mitochondriopathies has undergone substantial modification during the past few years because of increased knowledge of the genes involved. Mitochondriopathies are related either to a primary mutation in the mitochondrial DNA (mtDNA) with maternal inheritance or to a nuclear DNA mutation, especially in the polymerase gamma (*POLG*) gene (66). It is common, however, for both domains to be involved, and most *POLG* mutations are associated with multiple small deletions in the mtDNA. In a series of 25 neuropathies with a primary mtDNA mutation, 7 corresponded to mitochondrial encephalopathy, lactic acidosis, and strokelike episodes with the A3243G mutation and 9 to myoclonus epilepsy with ragged red fibers with the A8344G mutation. The neuropathy was not severe, and NB performed in 13 cases showed evidence of axonal or myelin modifications, with a few abnormal mitochondria identified by EM in some cases (67).

Paracrystalline inclusions in the Schwann cells of some unmyelinated fibers were first described in a case of Refsum disease by Fardeau and Engel (68) in 1969 (Fig. 15). They had been considered as modified mitochondria by several authors (9) but are commonly observed in various diseases and are not particularly numerous in proven cases of mitochondrial neuropathies. We, therefore, prefer to call them *Fardeau-Engel bodies* (69). Ironically, abnormal mitochondria are probably more numerous in neuropathies related to mitofusin abnormalities, observed in CMT-2A and CMT-4B.

A few cases of neuropathy caused by a *POLG* mutation have benefited from NB that showed a marked loss of nerve fibers (66). Muscle biopsy in such cases is also of interest because ragged red fibers and intramitochondrial crystalline inclusions may be detected by light microscopy and EM, respectively. In a similar manner, the autosomal recessive disorder mitochondrial neurogastrointestinal encephalomyopathy is caused by mutations in the thymidine phosphorylase gene associated with multiple deletions in the mtDNA (70).

Metabolic and Nutritional Neuropathies

Nerve biopsy is not indicated in the diagnosis of the PN of nutritional causes, including the so-called *tropical neuropathies*, or in uremia except in very unusual circumstances of suspected overlapping etiologies. Acute, subacute, or chronic lesions of axonal PN are found in the specimens.

Diabetes

Diabetes mellitus is one of the main causes of PN, and the prevalence of PN among diabetic patients increases with time, particularly in non–insulin-dependent diabetes mellitus. Several patterns of PNS involvement are encountered in diabetic patients, including cranial neuropathy, mononeuropathy, mononeuritis multiplex, lumbosacral radiculoplexopathy, and symmetrical PN (71). Apart from mononeuropathy, the classical presentation is a painful, mostly sensory, axonal neuropathy with autonomic involvement. The histological findings in this situation usually consist of varying extents of axonal degeneration involving all fiber types with microangiopathic changes and occasional onion bulb formations. As a rule, NB is no longer indicated in this usual phenotype of diabetic neuropathy. More recently, the occurrence of CIDP has been reported in diabetic patients with a good response to immunomodulatory treatment (72). In such patients, early motor involvement may be prominent and nerve conduction findings usually indicate a predominantly demyelinating PN. Neurophysiological data are sometimes inconclusive, however, and NB findings may be required to confirm the diagnosis of CIDP. Interestingly, recent findings suggest that the expression of adhesion molecules in nerve samples may help distinguish CIDP from diabetic PN (73). In conclusion, indications of NB in diabetic patients are

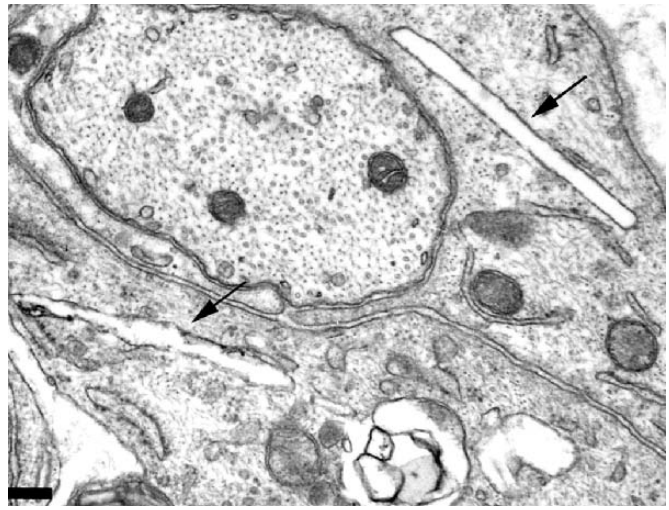

FIGURE 16. Electron microscopy of a nerve in Krabbe disease. There are several elongated inclusions in the Schwann cell cytoplasm (arrows). Scale bar = 500 nm.

TABLE 2. Summary of Clinical Situations When Nerve Biopsy May Be Very Useful or Indispensable for the Diagnosis

	Disease Groups	Condition	Comments on Nerve Biopsy
Acquired neuropathies	Immune-mediated neuropathies	Vasculitis	- diagnostic yield is variable and may be improved in combination with a muscle biopsy at the same site
			- may be particularly useful when vasculitis is confined to peripheral nerves
		CIDP	- may be helpful in patients with clinically atypical presentations or when nerve conduction studies are not diagnostic
		Neuropathy associated with monoclonal gammopathy	- may be extremely helpful to demonstrate: 1) presence of lymphomatous infiltrates 2) amyloidosis 3) endoneurial deposits (intramyelinic or interstitial)
			- exception: patients with IgM anti-MAG neuropathy
	Toxic neuropathies	Various drug-induced neuropathies, particularly those causing demyelinating neuropathies	- may help to differentiate a toxic neuropathy from other type of neuropathy, (e.g. amiodarone-induced neuropathy with electrophysiological features suggestive of CIDP)
Hereditary neuropathies	CMT syndrome	CMT-like presentation in sporadic cases	- may suggest a hereditary neuropathy in the absence of a family history
			- may direct the search for specific gene mutations in some cases (Table 1)
	Storage disorders	Storage disorders with peripheral nervous system involvement	- may reveal accumulation of abnormal material in Schwann cells or endothelial cells

CIDP, chronic inflammatory demyelinating polyneuropathy; CMT, Charcot-Marie-Tooth.

marginal, although histological findings may be decisive in selected cases to confirm a treatment-responsive PN.

Toxic PNs

Drugs

Amiodarone and chloroquine induce characteristic lesions of similar appearance: numerous polymorphous inclusions assuming a lamellar or pseudomyelinic appearance in Schwann cell cytoplasm of myelinated and unmyelinated fibers, fibroblasts, and endothelial cells (5, 6). The nerve lesions of most other neurotoxic drugs exhibit nonspecific axonal involvement, which may be difficult to distinguish from lesions induced by the disease for which they have been prescribed, as previously mentioned with respect to AIDS PN.

Industrial Agents

Several industrial chemicals and solvents can lead to PN. Only a few such as n-hexane, methyl n-butyl ketone, acrylamide produce characteristic ultrastructural lesions; some axons are distended by proliferations of 9- to 10-nm-diameter filaments.

Other Causes

Occasionally, NB can disclose an unsuspected storage disease (e.g. neurolipidosis) based on its characteristic morphological features (5, 9, 11) (Fig. 16). Adult polyglucosan body disease involves the CNS and PNS with intraaxonal accumulation of round structures consisting mainly of entangled filaments (74). The diagnosis can be made on NB because enlarged myelinated fibers are readily seen in semithin sections. A deficiency of glycogen branching enzyme (GBE) with a homozygous missense mutation of the *GBE* gene is found in Ashkenazi Jewish patients and heterozygous mutations are found in other patients (75), corresponding to glycogenosis Type IV.

CONCLUSIONS

Nerve biopsy, as described herein, is still very useful in a wide range of conditions, although molecular genetic and neurophysiological findings are diagnostic in an increasing number of genetic and immune-mediated neuropathies, respectively. Although determination of intraepidermal nerve fiber density (e.g. by immunostaining for protein gene product 9.5) in skin biopsy samples may help confirm the diagnosis of small-fiber neuropathy, it does not help understanding the pathogenic mechanism of nerve injury or the etiology of a polyneuropathy (76). Specific patients with diseases such as peripheral nerve vasculitis, amyloidosis, and leprosy, and with extremely variable clinical presentations may benefit from NB (77). Nevertheless, nerve biopsy must be considered on a case-by-case basis because the results may help confirm a suspected diagnosis and/or guide the therapeutic strategy (78). Some of the conditions in which NB findings are frequently helpful are listed in Table 2.

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