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ORIGINAL COMMUNICATION

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Neurophysiological studies in malignant disease with particular reference to involvement of peripheral nerves

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Abstract Neurological and neuromuscular disorders are frequent complications in patients with neoplasms and may involve the neuromuscular system, including motor and sensory nerve cell bodies, axons, myelin, neuromuscular transmission and muscle alone or in combination. Electrophysiological studies are of value in delineating the type, degree and extent of involvement, and may be of assistance in pointing towards the underlying cause: paraneoplastic factors, treatment with chemotherapy or radiation or metastatic infiltration. Though some electrophysiological features may be characteristic of certain syndromes, they rarely can stand alone but require clinical, pathological, radiological, and laboratory studies to obtain a diagnosis. Even in cases where such studies are obtained, a final diagnosis may only be ascertained during follow up, since the neuromuscular disorders frequently occur before the neoplasm is detected.

Key words Neoplasm · neuromuscular disorders · chemotherapy · radiation · paraneoplastic disorders · EMG · nerve conduction studies · peripheral nerve

Introduction

Both the central and the peripheral nervous system, the neuromuscular transmission, and striated muscle may be affected by malignant disease [1] and neurological symptoms occur in 15–20 % of patients with cancer [2]. The neurological complications may occur in the course of the cancer disease or before the malignancy has been recognized. The primary aim of neurophysiological studies is to delineate the type and extent of the neuromuscular involvement since these complications may influence morbidity and prognosis in addition to the effects of the malignant disorder itself.

The purpose of this review is to describe the electrophysiological features of peripheral nerve disorders in patients with malignancies and to delineate main differential diagnostic considerations.

Classification of neuromuscular syndromes

Neurological complications from cancer (Table 1) may be due to (1) metastatic invasion of nerves, nerve plexus [3], or meninges (leptomeningeal carcinomatosis, cf. [4]), (2) treatment with radiation [3] or chemotherapy [5], and (3) as remote effects of malignant disease affecting nerve, muscle or neuromuscular transmission [6, 7].

Usefulness of electrophysiological studies

Electrophysiological investigations have a central role in the detection and characterization of pathological changes in the neuromuscular system (Table 1). By combining key features it is possible to obtain strong evidence of the involvement of neuronal cell bodies, nerve

Table 1 Neuromuscular disorders in cancer

Mechanism	Affected structures	Main pathophysiological features
Neoplastic invasion or compression	Peripheral nerve or brachial and lumbosacral plexus	Electrophysiological evidence of axonal degeneration
	Leptomeningeal metastases (carcinomatosis)	Electrophysiological signs of motor fiber degeneration
Chemotherapeutic agents (Vinca alkaloids, Cis-platin, Taxol, Suramin)	Peripheral nerve (polyneuropathy)	Motor and sensory axonal degeneration (vinca alkaloids, taxol)
		Dorsal root ganglion degeneration (cis-platin) with electrophysiological signs of sensory fiber degeneration
		Signs of demyelinating neuropathy (suramin)
Radiation therapy	Brachial or lumbosacral plexus	Anatomically delimited electrophysiological evidence of axonal degeneration (EMG shows fasciculations and myokymia)
	Myelopathy	Evoked potential signs of spinal cord involvement
Remote effects of cancer (paraneoplastic manifestations)	Peripheral nerve involvement	Sensorimotor axonal degeneration
	Dorsal root ganglion	Symmetrical or asymmetrical sensory axonal loss
	Anterior horn cell	EMG signs of loss of motor neurons
	Terminal axon affection	Neuromyotonia
	Neuromuscular transmission	Lambert-Eaton syndrome
	Skeletal muscle	Myopathy

roots, axons, or myelin in patients with clinical signs of peripheral nerve disease. It is, however, also evident that several interrelated structures may be affected by the disease process, as for example secondary axonal loss in demyelinating neuropathy or possibly primary involvement of both axons, neuromuscular transmission and striated muscle in cancer.

The pathophysiological changes are rarely specific for particular etiological entities and the findings cannot as a rule stand alone. Additional radiological and other imaging studies are usually necessary, and laboratory studies may reveal the presence of specific antibodies in sera or cerebrospinal fluid in paraneoplastic disorders [8], or the presence of gammopathy in hematological malignancies.

It is furthermore important to consider that neuromuscular syndromes in malignant disease may have features that are indistinguishable from disorders with non-malignant causation.

Peripheral nerve involvement in malignant disease

Nerve lesions may be classified according to the distribution of involvement, the mechanism of nerve damage, the pathological features and the electrophysiological findings (Table 2).

Table 2 Classification of peripheral nerve lesions in cancer

Category	Etiology	Structures involved
Focal nerve lesions	Neoplastic invasion/compression	Lumbosacral and brachial plexus
	Radiation treatment	Lumbosacral and brachial plexus
	Paraneoplastic manifestation	Brachial plexus
	Vasculopathy or paraneoplastic lesions	Asymmetrical involvement of axons
Polyneuropathies	Chemotherapy	Sensory or both sensory and motor fibers
	Paraneoplastic manifestation	Sensory and motor fibers
		Sensory ganglion
		Anterior horn cells or motor axons
		Autonomic nerve fibers

Focal nerve lesions

Lumbosacral and brachial plexus affection

Brachial and lumbosacral plexopathy in patients with cancer may be due to metastatic spread or direct invasion or may be caused by irradiation, and distinction between the different causes may be clinically difficult. Plexopathy caused by tumor invasion or irradiation is usually progressive in nature and often severe.

Neoplastic invasion of nerve. Metastatic spread of malignancy to peripheral nerves and plexus usually occurs via lymphatic drainage [3], by direct cancerous invasion, or rarely by hematogenous spread [9]. The cancer types usually affecting the brachial plexus include breast or lung carcinoma, but other types of cancer, including sarcoma and lymphoma, may involve the brachial plexus [3]. Rare cases of paraneoplastic brachial plexopathy have been described in Hodgkin's disease [10].

Distinguishing clinical features include pain at presentation being much more frequent in malignant spread than in radiation induced damage [11], and the interval between treatment and the development of plexopathy is typically longer if caused by irradiation than by malignant spread [3, 12]. In Kori et al.'s [3] series the lower part of the brachial plexus was more often involved in neoplastic plexopathy whereas the involvement caused by radiation was more diffuse, though this has in other studies not been found to be a distinguishing feature [13, 14]. Horner's syndrome occurs frequently in neoplastic brachial plexopathy and it is considered to be due to growth into spinal nerves or roots. Magnetic resonance imaging shows abnormalities both in patients with neoplastic and radiation induced brachial plexopathy but the presence of a mass adjacent to the plexus has been found to be predictive of tumor infiltration [14].

Radiation treatment. The interval between irradiation and plexopathy is from months to years [3]; in experimental animals, the latency of pathophysiological changes after intraoperative radiation was $1^1/_2$–2 years depending on the dose [15]. The incidence of brachial plexopathy was 5 times higher in patients receiving 6300 cGy compared with 4800 cGy. Brachial plexopathy is considerably more frequent than lumbosacral plexopathy, which was described in only four of 2410 patients treated with irradiation of the pelvic cavity with isodoses of 7000–8000 cGy to the plexus [16]. Radiation-induced brachial plexopathy may occur at lower doses in patients treated with adjunctive chemotherapy [17].

Plexopathy occurring within months after treatment may be due either to the malignancy or to radiation. In rare cases, acute lumbosacral plexopathy was described in close association with radiation [18], and acute ischaemic brachial plexopathy associated with involvement of the subclavian artery has been described more than 20 years after radiation [19].

A central feature in irradiation-induced neuropathy is damage to the microvasculature of vasa nervorum, suggesting that ischemia may play an important role in the causation [20].

Electrophysiological findings. The most characteristic features of EMG findings, which occur in 60–70 % of patients with radiation-induced nerve damage include fasciculations and myokymia [13, 11, 21–23] with spike frequencies of 11–60 Hz, which is similar to that seen in other causes of myokymia where focal nerve damage is considered the eliciting factor [12]. In addition most patients with either radiation or neoplastic plexopathy have signs of chronic partial denervation on EMG with denervation activity and signs of reinnervation with prolonged, enlarged motor unit potentials. The post-radiation motor changes in some patients with lumbosacral abnormalities are considered to be due to anterior horn cell involvement at the lower spinal cord or caudal roots (for discussion see [16, 24]).

Nerve conduction studies reveal variable axonal loss with reduced amplitudes of compound sensory and motor action potentials in both neoplastic and radiation induced plexus lesions (Fig. 1). However, in addition, patients with myokymia after radiation may show signs of conduction block [12, 25, 26], suggesting additional demyelination [15]. Focal abnormalities in myelin associated with conduction block and fasciculations and myokymia are characteristic findings in chronic inflammatory demyelinating neuropathies [27, 28]. Electrophysiological studies using magnetic stimulation have suggested that non-symptomatic patients treated with radiation may show subclinical signs of axonal loss [22].

Polyneuropathies

Neuropathy due to chemotherapy

Anti-neoplastic drugs that cause peripheral nerve affection include primarily platinum compounds, vinca-alkaloids, taxanes, suramin, and dolostatin [5]. The dose dependent neurotoxic side-effects are major limiting factors of sufficient treatment in patients with a variety of cancers [29, 30] and has led to thus far unsuccessful trials of administration of different growth factors with potential protective effects on peripheral nerve [31].

The toxic effect of cisplatin is associated with sensory axon degeneration, and probably occurs at the dorsal root ganglia [32] possibly through interference with protein synthesis [33]. In addition cisplatin may interfere with axonal transport through binding to microtubules [34]. The electrophysiological findings include

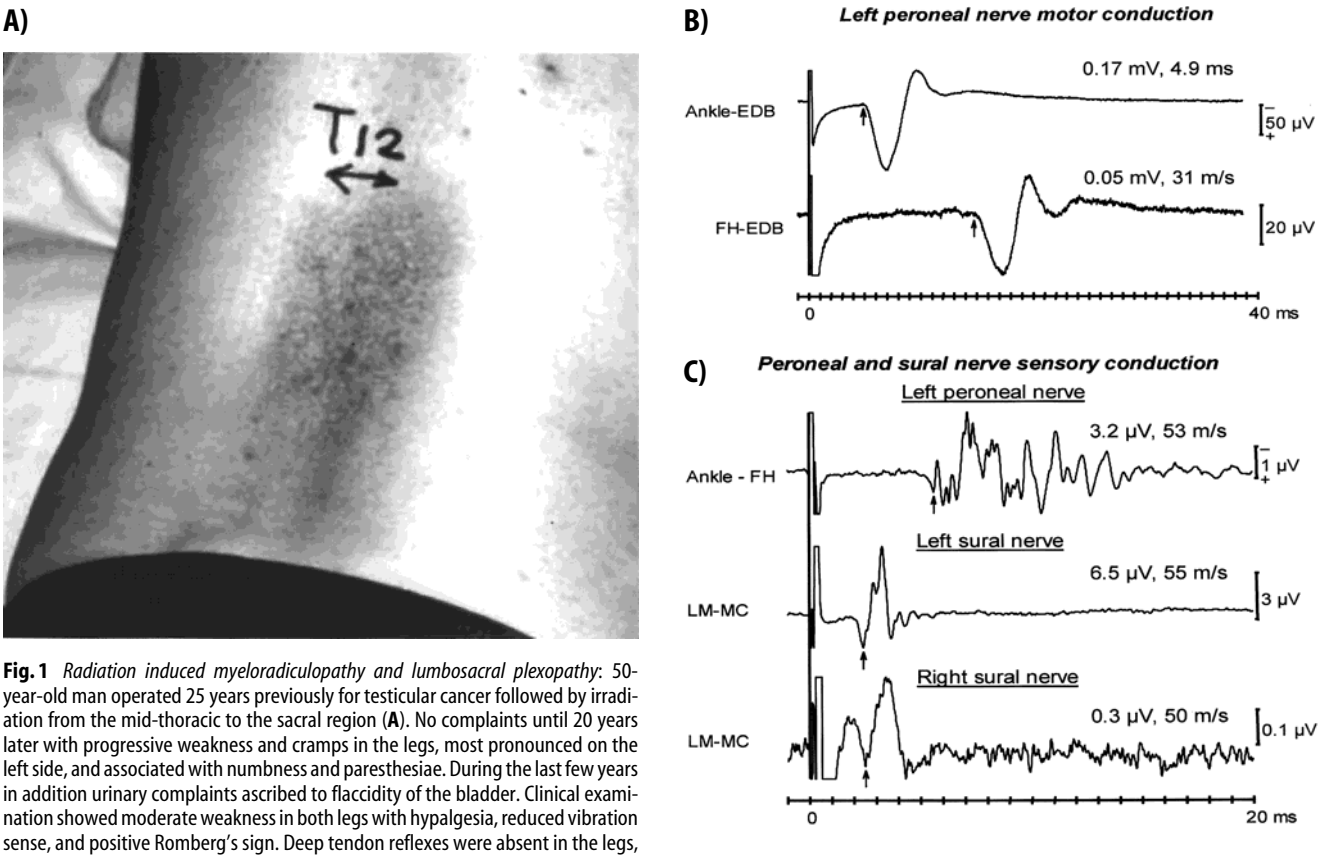


Fig. 1 *Radiation induced myeloradiculopathy and lumbosacral plexopathy*: 50-year-old man operated 25 years previously for testicular cancer followed by irradiation from the mid-thoracic to the sacral region (**A**). No complaints until 20 years later with progressive weakness and cramps in the legs, most pronounced on the left side, and associated with numbness and paresthesiae. During the last few years in addition urinary complaints ascribed to flaccidity of the bladder. Clinical examination showed moderate weakness in both legs with hypalgesia, reduced vibration sense, and positive Romberg's sign. Deep tendon reflexes were absent in the legs, and the plantar reflex on the right was extensor in type. EMG showed signs of severe chronic partial denervation of the left medial vastus and anterior tibial muscles. The motor conduction of the left peroneal nerve showed severe loss of motor fibers (**B**), normal sensory conduction of the left peroneal nerve, mild reduction of the left sural nerve action potential, and severe reduction of the right sural nerve potential (**C**). The spinal fluid showed raised protein at 110 mg%, and clinical and electrophysiological studies were consistent with a mixed lower spinal cord and right lumbosacral plexus disorder on the basis of radiation damage. This was confirmed by findings at motor evoked potentials, and the MRI of the spinal cord was normal.

reduction of the compound sensory action potential amplitudes with only mild changes in sensory conduction velocities, and histological evidence of severe loss of large myelinated axons, consistent with degeneration of dorsal root ganglion cells [35]. In addition there is electrophysiological evidence of spinal cord and brain stem involvement. Motor conduction studies showed only minor changes.

Similarly taxanes may cause a neuropathy through interference with microtubule function [36, 37]. Paclitaxel and Docetaxel, usually used in combination with cisplatin, cause a moderate sensory neuropathy [38, 39]. Also monotherapy with Docetaxel is associated with a dose-dependent predominantly sensory neuropathy [40]. Motor conduction changes have, however, been found in patients treated with paclitaxel [41].

The neuropathic effects of vinca-alkaloids have been shown in experimental animals and in humans [42, 43], and cause disruption of axoplasmic transport [44]. Vincristine treatment is associated with a distal sensorimotor neuropathy of axonal type, which usually is mild and reversible but may be associated with severe weakness [4].

Suramin is a polysulphonated, naphtylurea antiparasitic agent with effects on a number of refractory malignancies [45], and it has been found to cause either a length dependent axonal neuropathy or a demyelinating neuropathy with features of acute inflammatory demyelinating neuropathy in some patients [46].

Arabinoside treatment is associated with cerebellar symptoms. In rare cases high-dose treatment has been associated with demyelinating neuropathy with conduction block [47].

Paraneoplastic polyneuropathy

Paraneoplastic neuromuscular disorders are defined as remote effects of cancer not related to treatment or to deficiency states [48, 49] and often involve both the central and peripheral nervous systems alone or in combination [50]. In the peripheral neuromuscular system, the involvement may be localized to motor or sensory nerve cell bodies (neuronopathies), somatic or autonomic pe-

ripheral nerves, neuromuscular transmission or striated muscle (Tables 1, 2) [4, 51, 52].

The types of malignancy associated with paraneoplastic neuromuscular disorders include several solid tumors as well as hematological malignancies. Small cell carcinoma of the lung (SCLC) is by far the malignancy most often associated with paraneoplastic symptoms, and 60–75 % of patients with paraneoplastic neuromuscular disorders have SCLC [48]; in addition, thymoma, ovarian cancer, breast cancer, prostate cancer, and Hodgkin and non-Hodgkin lymphoma are associated with neuromuscular disorders [53, 54]. Neuropathy often precedes detection of the tumor by several months (average 26 months) [53, 55].

Other paraneoplastic disorders in lung cancer include weight loss, finger clubbing, fever, and endocrinopathies [56], which are more frequent than neurological involvement. Rare instances of nephrotic syndrome have been described [57].

Paraneoplastic involvement of peripheral nerve, neuromuscular transmission and striated muscle is now considered to be an autoimmune disorder [58], though the direct pathophysiological effect that auto-antibodies exert has been established only in a limited number of syndromes [59]. Thus, in Lambert-Eaton myasthenic syndrome (LEMS), myasthenia gravis, and Isaac's syndrome, antibodies have a direct pathogenic effect on appropriate ion-channels (Table 1) providing a mechanism for the disorder [60, 61].

The best characterized paraneoplastic peripheral neuropathy is subacute sensory neuronopathy (SSN) [2, 62] which often occurs in connection with raised titers of polyclonal IgG anti-nuclear neuronal antibodies (ANNA–1, anti-Hu) that share epitopes with malignant cells in SCLC [63]. The antigen is a RNA binding protein, and it is speculated that the antibody may interfere with RNA processing in neurons [8, 64]. The direct pathogenic effect of the antibody has been questioned, since transfer of the disease to experimental animals has been unsuccessful. A direct role has been suggested by the lytic effect of anti-Hu antibodies on CNS-cells in experimental animals [63], possibly via a T-cell related mechanism [65, 66]. As a diagnostic marker, a very high proportion of patients with sensory neuropathy or limbic encephalitis or both and anti-Hu antibodies have SCLC [67] though some patients with Sjögren syndrome have low titers of anti-Hu antibodies [63, 68]. A high proportion of patients with lung cancer have, however, neuronal antibodies without overt neuromuscular disease [69], and some patients have paraneoplastic neuropathy without raised antibodies [70, 71]. Anti-Hu may be associated with multiple neuromuscular syndromes including sensory and motor neuronopathy and Lambert Eaton syndrome [72], or combined sensory neuropathy and neuromyotonia in the same patient [73]. Sensory neuropathy associated with other anti-bodies such as anti-Purkinje cell antibodies have been described in breast cancer [74].

Anti-CV2 antibody (a group of paraneoplastic antibodies that react with a 66-kDa brain protein belonging to the family of Ulip/CRMP proteins) reacts with a subpopulation of oligodendrocytes in rodents and is associated with cerebellar degeneration, uveitis and peripheral neuropathy, and may occur alone or in combination with anti-Hu antibodies in SCLC. About half the patients have a sensorimotor peripheral neuropathy and the antibody reacts with peripheral axons [75].

Stiff-man syndrome is a rare disorder characterized by muscle rigidity, associated with deficiency of gamma-aminobutyric acid (GABA) due to antibodies against glutamic acid decarboxylase (GAD) [76]. However, a similar syndrome has been described in breast carcinoma associated with antibodies against amphiphysin I [63]. One of three patients with SCLC and antibodies against amphiphysin had muscle rigidity [77], and other studies have found raised titers in SCLC but no association with particular neurological syndromes [78]. Antibodies against GAD have, however, also been described in patients with LEMS with and without SCLC [79], and anti-amphiphysin antibodies have also been found in a patient without cancer [80].

The autoimmune etiology of paraneoplastic disorders raises the possibility that immunomodulation could ameliorate the neurological disorder. However, this has not been the case [55], and moreover tumor removal has not led to improvement of the neuropathy [81]. This lack of effect could, however, be due to the irreversible neuronal degeneration in these disorders (Fig. 2). Thus, treatment with intravenous immunoglobulin early in the course of neuropathy has led to improvement in some patients [82]. Recovery in a dog with tetraparesis and neuropathy after removal of a lung tumor [83], also suggests that improvement might be obtained if treatment is initiated before severe axonal loss has occurred.

Paraneoplastic sensorimotor neuropathy. The frequency with which polyneuropathy occurs in cancer is small [84], and depends on the type of underlying cancer and on the method of detection. If clinical criteria are used in cancer patients, only 1–5 % have paraneoplastic neuropathy [48, 51, 85]. About 30 % of patients are diagnosed with a paraneoplastic neuropathy when quantitative sensory testing is used [86], and 30–40 % when electrophysiological studies are carried out [87]. Estimates indicate that approximately 10–15 % of patients with peripheral neuropathy will eventually prove to have a paraneoplastic neuropathy. Both small and large sensory fibers may be involved [86], and frequently muscle weakness occurs in patients with predominant sensory neuropathy either due to additional motor involvement or to deficient sensory feed-back [67].

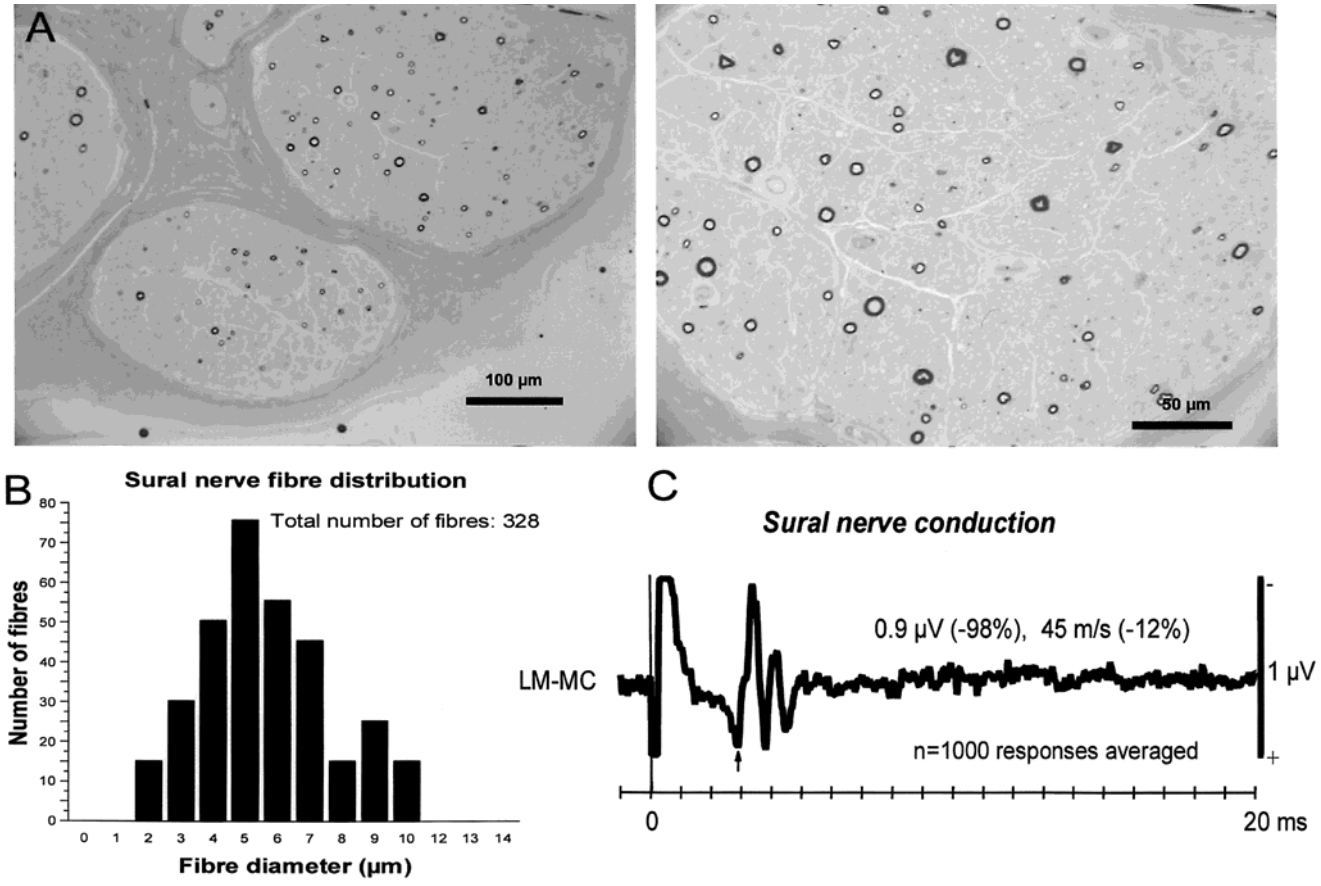


Fig. 2 *Subacute sensory neuronopathy (probably on the basis of autoimmune disease)*: 47-year-old woman with a history of ulcerative colitis, arthritis and sclerosing cholangitis, and a family history of thyrotoxicosis in her paternal grandmother and rheumatoid arthritis in her father. Over a period of about one year progressive loss of balance when walking. Muscle power mildly reduced in arms and legs, gait broad based, Romberg positive. Reflexes were hyperactive. EMG did not show evidence of denervation (deltoid, brachial biceps). Conduction studies showed normal motor conduction of the median, ulnar and peroneal nerves, and severely reduced amplitudes of sensory potentials in these nerves. The sural nerve action potential was severely reduced (**C**). A sural nerve biopsy showed severe loss of fibers and absence of regeneration (**A**), and the morphometry showed only 328 fibers left with loss of all fiber diameters (courtesy of H. Schmalbruch, MD, with permission from Oxford University Press).

Mild neuropathy frequently occurs during the course of the malignancy; in cases where the neuropathy precedes the malignancy, the course of the neuropathy is often severe progressive or relapsing [88].

Polyneuropathy occurs frequently in patients with monoclonal gammopathies in the context of malignant disease including multiple myeloma with amyloid deposition, and osteosclerotic myeloma with demyelinating motor and sensory involvement [89]. In some patients with monoclonal gammopathy the neuropathy occurs in a multiorgan syndrome in connection with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes) [90, 91], and with anti-MAG (myelin associated glycoprotein) associated demyelinating polyneuropathy in Waldenström's macroglobulinemia [92].

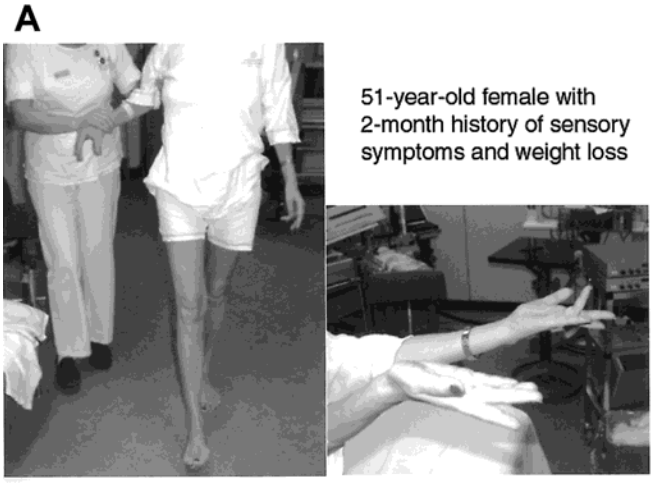
In 8 % of patients with malignant lymphoma there is clinical evidence of mild neuropathy, whereas 35 % have nerve conduction abnormalities, and the sural nerve shows signs of axonal degeneration and in some demyelination [93]. In other studies the prevalence of peripheral neuropathy is smaller but in patients with Hodgkin's disease [94] or non-Hodgkin lymphoma [95] an association to Guillain-Barré syndrome and chronic inflammatory demyelinating neuropathy has been seen. Paraneoplastic peripheral nerve disorders are considered to occur in 2–3 % of patients with Hodgkin's disease and include sensory or motor neuronopathy and brachial plexopathy [10].

Electrophysiological findings Trojaborg et al. [87] found denervation activity on EMG examination in 30–40 % of patients with lung cancer without of neuromuscular symptoms indicating subclinical neurogenic changes. Only a few patients showed abnormalities at nerve conduction studies in that study as well as in the study by Lenman et al. [96], whereas other studies showed a mild mixed peripheral neuropathy in 18 % with lung cancer and 10 % with lymphoma [97]. Simi-

larly a high proportion of patients with lung cancer have histological evidence of subclinical myopathy [98]. Furthermore, EMG studies in patients with malignancy have shown frequent non-specific abnormalities that suggest the presence of a "neuromyopathy" [6, 99, 100].

Paraneoplastic sensory neuropathy. *Clinical findings* Subacute sensory neuronopathy (SSN) is a well-characterized syndrome with subacute sensory loss, hyperalgesia, and ataxia that often develops asymmetrically but in its severe form may render the patient unable to stand due to proprioceptive sensory loss with pseudoathetosis (Fig. 3) [2, 51]. A minority of patients have an indolent course [103]. A large proportion of patients with paraneoplastic SSN have additional evidence of encephalomyelitis [8, 67], and may have associated autonomic and cerebellar disorders [81]. Weakness is rarely prominent though motor involvement has been described [104] and atrophy and hypotonia often occurs. The differential diagnosis includes other causes of sensory neuropathies in connection with HIV infection, Sjögren syndrome, gammopathy in particular associated with anti-MAG [105]. In a prospective study of 51 patients with sensory neuropathies of unknown cause, 19 patients eventually were found to have cancer of various types including hepatoma, lymphoma, SCLC, bladder cancer, prostate cancer, breast cancer and others with a mean interval of 28 months (range 3–72 months) between onset of neurological symptoms and diagnosis of the neoplasm [106]. The neuropathy may be asymmetrical with features of mononeuritis multiplex with intestinal pseudo-obstruction [107].

Electrophysiological findings Nerve conduction studies show severely diminished sensory potentials, with mildly reduced conduction velocities, or absent responses consistent with loss of mainly large fibers



D

Nerve	CSAP		CMAP	
	Amplitude	SNCV	Amplitude	DML/MNCV
Median	-97%	-22%	N	N/-18%
Ulnar	-98%	N	N	N
Peroneal	-80%	-18%	N	N/-21%
Sural	-99%	N		

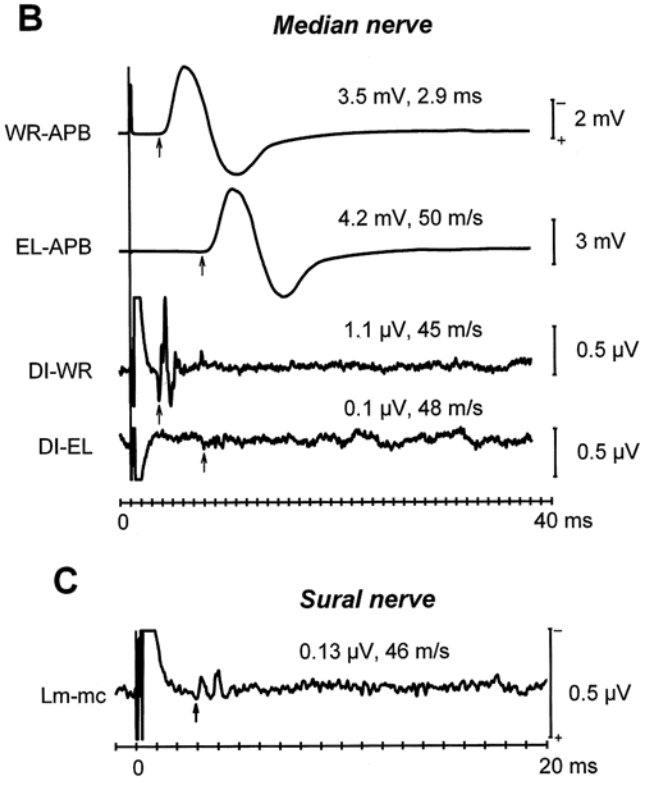
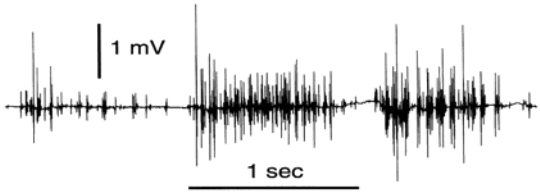


Fig. 3 *Subacute sensory neuronopathy*: 51-year-old woman with 2-month duration of progressive sensory symptoms with paresthesiae and numbness of the fingers, loss of motor control of the hands, and unsteadiness when walking. She had a weight-loss of 18 kg, and complained of depression leading to increased alcohol consumption. Subsequently she appeared increasingly demented. PET-scanning of the lungs revealed a suspect area of malignancy, but CT did not show evidence of pulmonary tumor. Anti-Hu and -Yo antibodies were negative. CSF examination showed normal protein and cells, ANCA and ANA were negative. On examination she needed support when walking, and she displayed pseudoathetosis of her fingers (**A**). She could stand on toes and heels, Romberg was markedly positive, and she had severe loss of vibration and position sense at the fingers and toes. Ankle jerks were absent, but knee jerks and tendon reflexes of the upper extremities were present. EMG showed minor unspecific abnormalities with reduced recruitment at maximal effort. Conduction studies of the right median nerve showed normal CMAP amplitudes, mildly decreased motor conduction velocity, and severe reduction of the sensory potentials from digit I and III (**B, D**). The peroneal and ulnar nerves showed normal motor conduction and severe reduction of the sensory potentials (**D**), and the sural nerve action potential was severely reduced (**C, D**).

(Fig. 2) whereas the motor conduction velocities and in most cases the amplitudes of the motor responses are normal. EMG shows normal motor unit characteristics and no denervation potentials in most patients, even in those with weakness, indicating that the motor symptoms may be secondary to loss of afferent control (Fig. 4).

Paraneoplastic motor neuron disease. Motor neuron involvement may occur in patients with neoplasm but is a rare phenomenon [1, 101]. However, EMG studies showing both signs of myopathy and denervation and fasciculations were considered to be partly due to motor neuron involvement [102], and the weakness in Denny-Brown's [62] cases with sensory neuronopathy was thought to indicate additional motor neuron affection. In larger epidemiological studies, no association between malignancy and motor neuron disease was found.

A



B

Abd . Poll. Brev . muscle	Denervation	MUAP duration	MUAP amplitude	Polyphasic MUPs
Force 3/5 Atrophy +	None	Normal	Normal	7%

C

Nerve	CSAP		CMAP	
	Amplitude	SNCV	Amplitude	DML /MNCV
Median	-98%	-28%	-71%	N/ -19%
Peroneal	-85%	N	N	N
Sural	-89%	N		

Fig. 4 *Subacute sensory neuronopathy*: 65-year-old woman with 3–4-month duration of progressive painful dysesthesia of the fingers, loss of sensation in the fingers and feet, and loss of balance. Had been a heavy smoker for many years. No symptoms from the cranial nerves. On examination severe loss of vibratory and position sense at fingers and toes, severe hypesthesia and hypalgesia of arms and legs. The distal muscles in the hands were weak, mild atrophy, normal force proximally in the arms, and normal force in the legs. Deep tendon reflexes were absent. She had increased excretion of uroporphyrins (consistent with porphyria cutanea tarda), liver biopsy showed cirrhotic changes consistent with hemochromatosis. ANA negative, ANCA mildly positive, anti-Hu and -Yo negative. PET scan showed no changes consistent with malignancy. EMG of the left abductor pollicis brevis muscle showed severely abnormal recruitment of motor units (**A**), but activity at rest and analysis of motor unit potentials (MUP) did not show signs of denervation (**B**). Conduction studies of the left median nerve showed mild reduction of the CMAP amplitude, and severe reduction of the sensory potentials (**C**). The peroneal nerve showed normal motor conduction and severe reduction of the sensory potential (**C**), and the sural nerve action potential showed reduced amplitude (**C**).

Mononeuropathy multiplex. Peripheral nerve involvement may occur as a consequence of ischemia due to vasculopathy in patients with lymphomas [93, 94, 108]. The neuropathy is due to sensorimotor axonal degeneration in a polyneuropathic, mononeuropathic, or multifocal distribution.

Paraneoplastic neuropathy may be asymmetrical with features of mononeuritis multiplex with intestinal pseudo-obstruction [107], and vasculitis is found in rare cases [52, 109–111].

The electrophysiological findings depend on the stage of the disorder. Early in the disease, individual nerves or highly asymmetrical signs of axonal loss are characteristic, whereas at later stages confluent abnormalities in several nerves may be the characteristic features.

Conclusions

Whereas the electrophysiological studies are indispensable in demonstration of the degree, type, and distribution of pathological changes, the findings in themselves do not allow diagnosis of the underlying etiology, and hence cannot be used to show that a particular neuromuscular disorder is associated with a neoplasm. Thus, although motor neuron disease, motor neuropathy, mixed axonal neuropathies, sensory neuronopathy, mononeuritis multiplex, acute and chronic demyelinating neuropathies, neuromuscular transmission disorders, stiff-man syndrome, and neuromyotonia occur in connection with various types of neoplasms, they also occur in patients without neoplasms. This requires a multidisciplinary approach to these disorders that include radiological, biochemical, histological or immunohistochemical and in some cases molecular biological methods. Furthermore, though some disorders are strongly related to the presence of particular immunological markers, others with both malignant and non-malignant variants may have the same immunopathological profile and the neurological disorder may occur before the neoplasm is detected. Finally, in for example neuropathies associated with gammopathy of unknown significance (MGUS), the hematological disorder may transform into a malignant disorder [112, 113]. These factors markedly complicate the diagnosis of paraneoplastic neuromuscular disorders.

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