Other Diagnostic Tools for Neurological Disease in Cancer: EEG, EMG, and Lumbar Puncture

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Electroencephalography

History

The early works of Galvani and Volta were essential in the discovery of animal and later human electrical circuitry in the nervous system [1]. In 1875, British physician Richard Caton received a grant to explore electrical phenomena in the exposed cerebral hemispheres of monkeys. Caton found that "feeble currents of varying directions pass through the multiplier when the electrodes are placed on two varying points of the external surface." [2] In 1924, Hans Berger performed the first electroencephalogram (EEG) on a human when he performed an EEG on a 17-year-old boy during an open neurosurgical operation. Throughout the 1930s Berger continued to describe different patterns, but it was the work of American pioneers Fredric Gibbs, Erna Gibbs, Herbert Jasper, and William Lenox that defined what we know today about epileptogenic discharges and their role in epilepsy [1, 3]. Recent advances have helped to further the field of epilepsy. While the first EEGs were on paper, the advent of computers has made digitalized EEG easier to read and more accessible to the clinician. Additionally, video monitoring in conjunction with EEG has helped to further correlate semiology types with EEG findings. The discovery of electroencephalography was a milestone in the diagnosis and evaluation of patients with seizures and remains a valuable tool today.

Technical Component

In order to obtain an EEG, an EEG technician places scalp leads, records the EEG for a given amount of time, and transfers the data to a neurologist for interpretation. Most commonly with electroencephalography, scalp electrodes are placed with a gel or putty that makes an electrolyte bridge between the electrode and the skin. An electrical potential is generated between two given positions on the scalp and the signal is amplified via an amplifier and displayed on the computer screen as an upward or downward deflected wave. Ultimately, an EEG recording measures, amplifies, and registers differences between fluctuating electrical field potentials and displays this as a function of time. Frequencies and amplitudes are interpreted by the neurologist. Frequencies include delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (30–60 Hz) [1]. In adults, the normal wake state consists of alpha, while theta and delta frequencies are considered abnormal. Additionally, sharply contoured epileptiform discharges can be seen and are sometimes pathologic. In the most basic sense, a seizure is a rhythmic build up of epileptogenic discharges with evolution over space and time.

In order to localize pathology of a lesion, one must know where the electrodes are placed on the scalp. In an effort to standardize the recorded data, a committee of the International Federation of Societies for Electroencephalography and Clinical Neurophysiology recommended what is known as the International 10–20 system. This system requires specific measurements to be made from bony structures of the skull to determine the placement of electrodes in order to standardize inter-electrode distance in every patient [4].

An EEG has very good temporal resolution but lacks spatial resolution. Approximately 10 cm^2 of cortical surface must be activated in order to appreciate a response on scalp EEG. EEG has varied sensitivity and specificity. It is sensitive for discharges with a large field as seen in a generalized seizure but lacks sensitivity in small focal seizures.

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EEGs with spike and wave discharges can be relatively specific for certain epilepsy types, but generalized slowing and other patterns are relatively nonspecific in determining the causative source [5]. Thus, interpretation of the EEG should be made with the clinical context of the patient in mind.

Indications and Contraindications

Electroencephalography is a useful tool in the diagnosis of both clinical and subclinical seizures. It is most commonly used in evaluation of patients with suspected seizures but has other utility in the cancer patient. Overall, 20–40% of patients with brain tumors will present with seizures and another 20–45% will develop seizures later in the course of their disease [5–8]. Mental status changes, unresponsiveness, episodic spells, and shaking movements are frequent indications for EEG evaluation. There is mounting evidence that comatose patients, particularly those with structural lesions of the brain, should be monitored with continuous EEG for the evaluation of subclinical seizures. Nearly 10% of all comatose medical intensive care unit patients with no suspicion for seizure have non-convulsive seizures [9]. Up to one-third of patients with central nervous system infections have subclinical seizures [10]. In certain paraneoplastic encephalidities, up to one-half of the patients have seizures and even more have EEG slowing [11]. Supratentorial tumors can have rates exceeding these [8]. Thus, it is imperative that EEG has a low threshold for use as a diagnostic tool in the cancer patient.

There are no true contraindications to EEG. Placing electrodes over skin lesions on the scalp (due to surgical incision or ulcerations from prolonged EEG monitoring) should be avoided, but the electrodes can be placed on a nearby site if needed. EEG can be performed even with the presence of electrical devices such as a cardiac pacemaker, cochlear implant, or deep brain stimulator. Hair weaves or other extensions should be removed in order to allow direct contact between the electrodes and the scalp.

Slow EEG Patterns

Electrocorticography has strengths and weaknesses in evaluating the cancer patient. EEG is reliable at localizing lesions of the superficial cerebral hemisphere but is of limited use in deep lesions, particularly those in the posterior fossa. Tumors are electrically inert and destroy neurons thus augmenting the EEG recording. Studies have shown that direct electrocorticogram (ECog) evaluation of the cortex with the skull removed demonstrates (a) the cortex invaded by tumor has no activity, (b) the cortex abutting the tumor has a burst-suppression pattern, and (c) the most distant cortical zones have continuous slow waves [12].

A common pattern present with primary or metastatic brain tumors is continuous focal polymorphic delta slow activity due to focal lesions of the subcortical white matter. This slow activity is minimally reactive to different physiologic states and persists throughout wake, drowsiness, and even N2, N3 and REM sleep. This is often seen in tumors such as glioblastoma which disrupt subcortical and cortical structures [13].

Another pattern commonly seen is slow rhythmic sinusoidal monomorphic waves occurring in bursts. This intermittent rhythmic delta activity (IRDA) activity can have a frontal predominance (FIRDA) or occipital predominance (OIRDA); the occipital pattern being seen primarily in children. This intermittent monomorphic activity, in contrast to polymorphic delta activity, is much more widespread over bilateral hemispheres and shows reactivity with augmentation with eye closure, hyperventilation, and drowsiness. IRDA ceases during deeper non-REM sleep and reappears in REM sleep. With infratentorial lesions, this IRDA is typically symmetric and bilateral with some shifting asymmetry. With supratentorial lesions, however, this IRDA can show a persistent asymmetry being most prominent over the side of the lesion [13].

Yet another pattern often seen with focal lesions such as primary or metastatic brain tumors is attenuation, or a decrease in amplitude often with drop-out of faster frequencies. It is typically localized to the side of the lesion and can be widespread in distribution over the hemisphere. Attenuation can also be widespread over both hemispheres, and when severe, can become suppressed constituting a burst-suppression pattern [13].

Cancer patients with focal lesions can also have diffuse changes on EEG due to a variety of toxic-metabolic entities. At times, EEG can provide objective criteria for severity of the underlying pathologic process. Table 3.1 lists some common toxic-metabolic derangements that are seen in cancer patients and their EEG findings.

Paroxysmal and Ictal EEG Patterns

According to the International Federation of Societies for Electroencephalography and Clinical Neurophysiology (IFSECN), a transient is an event that clearly stands out against the background EEG and can be a single wave or a sequence of two or more waves. Spikes are transients which are considered epileptiform and are clearly distinguished from the background with a pointed peak and duration between 20 and 70 ms and a sharp wave is a transient clearly distinguished from the background with a pointed peak and duration between 70 and 200 ms [14]. Spikes and sharp

Table 3.1 Common toxic-metabolic derangements in cancer patients and their associated EEG findings

Derangement	EEG findings
Benzodiazepine or barbiturate use	Diffuse beta activity
Hepatic failure	Early—slowed alpha rhythm
	Late—persistent theta or delta activity
	Triphasic wave pattern—2–4 Hz bilaterally synchronous waves with a triphasic morphology
Renal failure	Early—slowed alpha rhythm
	Late—nearly persistent theta or delta activity
	Triphasic waves—also present
Hyponatremia	Early—slowposterior alpha rhythm
	Late—generalized slow activity
	High-voltage IRDA
	Epileptiform discharges are uncommon even with seizures
Hypernatremia	Theta activity
	Often no EEG changes at all
Hypoglycemia	Enhanced response to hyperventilation with FIRDA longer after cessation of hyperventilation
	Glucose 50–80 mg/dl: slowing of alpha rhythm
	Glucose below 40 mg/dl diffuse theta and delta with IRDA activity
	Epileptiform discharges are uncommon even with seizures
Hyperglycemia	Changes typically not seen until glucose greater than 400 mg/dl
	Sporadic epileptiform discharges
Hypothermia	Core temperature 29–30 °C—diffuse theta and delta
	Core temperature 20–22 °C—burst suppression pattern
	Core temperature <18 °C—electrocerebral silence

waves are closely related phenomenon, both of which are associated with an epileptic seizure disorder, although both transients may occur with no prior history of epileptic seizure disorder [1]. These epileptiform and highly epileptogenic potentials are seen in patients with and without structural brain lesions. These discharges are often seen interictally in patients with brain tumors and epilepsy. They are often localized to the region of the brain tumor but in multifocal structural lesions such as brain metastasis, multifocal epileptiform discharges can be seen. It is uncommon for this epileptiform activity to be the only EEG abnormality associated with a tumor. Typically, some degree of focal slowing is present when epileptiform activity is present [13, 15].

While epileptiform activity is commonly seen with indolent or static lesions, periodic lateralized epileptiform discharges are more commonly seen with an acute lesion [13]. Periodic lateralized epileptiform discharges (PLEDs) are sharp waves, spike waves, or more complex wave forms recurring periodically every 1–2 s with a return to background between discharges and occupying a relatively large area of the hemicranium [13, 16]. They can be due to a variety of structural lesions including neoplasms, hematomas, and infections. While stroke is the most common etiology of PLEDs, 12% of patients with PLEDs have brain tumors, almost all of which are supratentorial brain tumors. PLEDs are considered to be on the ictal-interictal spectrum and are highly associated with conversion to frank seizure activity. Almost 50% of patients with brain tumors and PLEDs have seizures [16].

When a patient has a seizure that persists for a sufficient length of time or repeats frequently enough that recovery between attacks does not occur, it is termed status epilepticus. Mortality with status epilepticus is up to 20%. Convulsive status epilepticus accounts for nearly half of all status epilepticus [17]. Over 4% of patients who present with status epilepticus have brain tumors. In patients who present with status epilepticus with no preexisting history of seizure, almost 9% have brain tumors [18]. Patients with structural brain lesions more often have refractory status epilepticus and over 5% of patients presenting with refractory status epilepticus have this condition secondary to a brain tumor [19].

At times, status epilepticus is partial (as opposed to generalized) in nature. Epilepsia partialis continua is a partial somatomotor status epilepticus that is often seen in the

setting of brain tumors. Between 11 and 15% of patients who present with epilepsia partialis continua have brain tumors as the etiology. EEG findings with this can be variable depending on the area of focus and, at times, the EEG can be normal given that it takes a sufficient amount of cortex to elicit a response on EEG [20, 21].

A common cause of altered mental status in the brain tumor population is non-convulsive status epilepticus (NCSE). NCSE can be defined as status epilepticus with reduced or altered consciousness, behavioral and vegetative abnormalities, or subjective symptoms with no major convulsive movements [22]. NCSE is the cause of altered mental status in over 5% of tumor patients [23]. NCSE is more common in patients with gliomas than in those with metastatic tumors [24]. Even in patients with systemic cancer but no brain metastasis, NCSE was the cause of altered mental status in 6% of patients [23]. EEG monitoring can be particularly helpful in the diagnosis of seizures in these patients and should be utilized in any cancer patient with altered mental status [25].

EEG Changes by Tumor Type

EEG changes in patients with brain tumors depend on several factors, including location, size, and growth rate. Although EEG patterns are not specific for the histologic pathology of the tumor, some general correlations can be made.

Extra-axial tumors that are slow growing, like meningiomas, are less likely to produce EEG abnormalities. Meningiomas located in the convexities, especially parasagittally, are more likely to cause changes like focal theta, FIRDA, and diminished or altered frontal beta rhythms. Rolandic meningiomas cause epileptiform discharges in up to 45% of patients with similar incidence of seizure. Meningiomas of other regions are less likely to cause EEG effects; however, approximately 25% of patients with meningiomas present with seizures [26, 27].

Indolent gliomas are more likely to cause EEG changes. Glioneural tumors including gangliogliomas and dysembryoplastic neuroepithelial tumors (DNETs) have the highest rates of epilepsy with 90–100% of patients having seizures, often pharmacoresistant [8, 28]. Diffuse low-grade gliomas cause seizures in 60–88% of patients [8, 29]. Focal polymorphic slow activity is usually a later finding and can occur intermittently. This slowing becomes increasingly persistent as the tumor progresses [30].

Rapidly growing parenchymal tumors, such as glioblastomas, are more likely to cause marked abnormalities on EEG but are less likely to cause seizures. Glioblastomas and other rapidly growing and destructive tumors cause prominent and focal polymorphic delta activity with marked alterations of background rhythms unilaterally and often bilaterally. Areas of necrosis can be electrically silent causing regions of attenuation. FIRDA occurs more frequently in glioblastoma than in other types of supratentorial tumors. With glioblastoma, epileptiform discharges are not present as frequently as they are with more indolent gliomas but PLEDS are more likely to occur [13]. Seizure rates in glioblastoma are approximately 30–50%, which is significantly lower than what is seen with lower grade gliomas [8, 31, 32].

Metastatic tumors to brain occur most commonly with cancers of the lung, breast, kidney, and melanoma. The EEG findings tend to be lateralized to the side of the metastasis. Larger or multiple metastatic lesions cause more EEG abnormalities than do small solitary lesions. The slow activity in metastatic lesions tends to be more theta range, compared to delta slow activity present with glioblastomas. EEG slow activity in metastatic disease also tends to be more episodic rather than persistent as seen with glioblastomas [33]. Metastatic lesions cause epileptogenic discharges in about one-third of patients and seizures in nearly one-half. Overall, metastatic lesions tend to cause more benign EEG changes than do gliomas of any grade [34].

EEG Changes by Tumor Location

EEG findings can vary by location of the tumor. Since the EEG reflects cortical neuron activity, hemispheric tumors affect EEG more markedly and reliably than do deeper tumors and tumors of the posterior fossa.

Frontal lobe tumors often cause local high-voltage delta slow activity. The slow activity can be continuous or episodic and bifrontal with a FIRDA pattern. FIRDA is more common with frontal tumors than in tumors of other locations. The background activity can be relatively preserved in frontal tumors. Epileptiform discharges are seen in almost one-half of frontal tumor patients [26].

Temporal tumors are the easiest to localize with EEG and display moderate to high-voltage focal polymorphic delta slowing lateralized over the tumor in over 80% of cases. In a majority of cases the slow activity is localized to the region of the tumor [33]. The slow activity recorded with temporal tumors tends to be continuous rather than intermittent. Temporal lobe tumors are also likely to cause FIRDA, but less so than frontal lobe tumors [26]. Background rhythms are more likely to be altered in posterior temporal lesions than in anterior temporal lesions.

Parietal tumors are less likely to cause EEG changes than are other supratentorial tumors. Slow activity can be local or more widespread and is more likely to be theta range, only of a moderate voltage, and intermittent or continuous. The background rhythms tend to be disturbed with parietal tumors [33].

Occipital tumors tend to cause focal polymorphic delta activity. Slow activity in surrounding temporal and parietal regions is often seen in conjunction with this. The posterior alpha rhythm is frequently absent ipsilaterally [1].

Tumors of subcortical structures vary in their findings and can be fairly non-localizing. Tumors of deep structures including the hypothalamus, fornix, basal ganglia, internal capsule, and corpus callosum characteristically cause intermittent slow activity. The slow activity is often monorhythmic and bilateral in an IRDA pattern [35]. Up to one-fourth of patients with lesions in these regions will have normal EEG findings [13]. Tumors of the sellar region typically do not cause EEG findings until they expand and obstruct the third ventricle, only then causing IRDA [36]. Thalamic tumors can cause IRDA but have also been shown to cause attenuation, disorganization of background frequencies, and slow activity of the ipsilateral alpha rhythm [37].

Tumors of the third ventricle and posterior fossa tend to be variable and are often normal on EEG. Abnormalities are more frequently found with obstruction of cerebrospinal fluid flow causing obstructive hydrocephalus. If an abnormal EEG is seen, the most common pattern is that of IRDA [1].

EEG Changes with Tumor Treatment

Iatrogenic changes are also seen on EEG in response to treatment therapies. Some are well characterized and others less so. EEG is useful in diagnosing epileptogenic potential with new cancer treatments and chemotherapeutic agents.

Brain irradiation occurs in two forms, whole brain radiation (WBRT) and partial brain radiation. WBRT can cause an acute or delayed reaction with cognitive decline and neurologic deficits. It can also cause generalized slowing of the background rhythms, IRDA, or even focal polymorphic delta slowing due to necrosis. Partial brain radiation can cause necrosis lending to focal slow activity, epileptogenic discharges, and even seizures [38–40].

Numerous medications for cancer treatment have an associated incidence of central nervous system toxicity. Some drugs cause diffuse dysfunction and slow activity on EEG while others are frankly epileptogenic. Table 3.2 lists known electrographic changes associated with common cancer treatments [41, 42].

EEG Changes with Autoimmune and Paraneoplastic Disorders

Paraneoplastic limbic encephalitis is becoming increasingly recognized with the commercial availability of antibody assays. Any paraneoplastic encephalitis involving the cortex or limbic system can cause EEG abnormalities and seizures. There are several autoantibody syndromes that are commonly associated with paraneoplastic epilepsy. These cause marked EEG abnormalities that are sometimes reversible with treatment of the underlying malignancy. Up to 100% of patients with paraneoplastic limbic encephalitis have an abnormal EEG, with seizures occurring in over 50% of these patients. EEG abnormalities include diffuse slowing, focal slowing, multifocal slowing, focal or multifocal epileptiform discharges, periodic lateralized epileptiform discharges (PLEDs), and seizures [43, 44]. Table 3.3 lists autoantibodies and their associated EEG findings [45–50].

Electromyography

History

The groundwork set by Alessandro Volta and Luigi Galvani paved the way for later visionaries in the field of peripheral electrodiagnosis [51, 52]. In 1833, Guillaume-Benjamin Duchenne used cloth-covered electrodes to stimulate nerves from the surface of the skin [53, 54]. Later, in 1850, Helmholtz successfully measured the conduction velocity of a nerve impulse of a frog, and later a human median nerve [54, 55]. In 1882, Wilhelm Erb devised a formula for polar contraction in normal and abnormal nerve states, and is generally cited as the founder of classic electrodiagnostics [54, 56]. On the electromyography front, a sensitive recording apparatus was needed for progress in the study of muscle action potentials. In 1922, Herbert Spencer Gasser and Joseph Erlanger overcame the limitations of a galvanometer with the advent of a cathode ray oscilloscope and laid the ground of the modern electrodiagnostic era [54, 57]. The first electromyogram (EMG) in a patient was performed by R. Proebster in 1928 and, following this, the field continued to expand into common clinical use [54, 58].

The demand for electrical testing of peripheral nerves grew with the two World Wars as physicians treating war casualties needed to know the extent of damaged nerves and the status of regeneration. This sparked a greater interest in the field and the need for peripheral diagnostics was realized. The First International Congress of Electromyography was held in 1961 in Pavia, Italy, and helped standardize values and the understanding of current peripheral electrodiagnostic studies [54]. Today, we continue to use electromyography and nerve conduction measurements to aid in the diagnosis of peripheral nervous system disorders.

Table 3.2 Cancer treatments and their associated EEG findings

Cancer treatment	EEG findings
Busulfan	Diffuse and focal delta
	Resolves within days of treatment discontinuation
	Seizures common and require prophylactic antiepileptic drug administration
Chimeric antigen receptor T-cell therapy	Slow background activity
	Epileptogenic discharges and increased seizure frequency
Cytarabine	Diffuse theta and delta activity
Ifosfamide	Slow alpha rhythm with increased theta and delta
	Triphasic waves
	Epileptogenic discharges and increased seizure frequency
	EEG and encephalopathy improve with benzodiazepine administration
Interferons	Diffuse theta and delta activity
	FIRDA activity
Methotrexate	Both diffuse and localized delta activity
	Seizure incidence increased
Pacitaxel	Diffuse theta activity
Vincristine	Diffuse theta and delta activity
	Epileptogenic discharges
	Increased seizure frequency with focal seizures

FIRDA frontal intermittent rhythmic delta activity

Table 3.3 Autoantibodies and their associated EEG findings

Antibody	Associated cancers	EEG findings
Anti-Hu	Small cell lung cancer	10% EEGs abnormal Temporal, bitemporal, or multifocal epileptiform discharges Seizures, epilepsia partialis continua, status epilepticus
Anti-Ma	Testicular germ cell tumor Breast cancer Non-small cell lung cancer	Epileptiform discharges Seizures and status epilepticus
NMDA	Ovarian teratoma	Irregular or rhythmic delta activity Extreme delta brush pattern Up to 70% with seizures or status epilepticus Tonic, focal, or generalized seizures
AMPA	Thymus Breast Lung	Temporal or bitemporal epileptiform discharges or seizures Diffuse, focal, or multifocal slow activity
GABA-B	Small cell lung cancer	Diffuse slow activity PLEDs Up to 100% with seizures
VGKC	Small cell lung cancer Often no tumor found	Temporal or bitemporal epileptiform discharges Faciobrachial dystonic seizures, tonic seizures, temporal seizures Diffuse slow activity

NMDA N-methyl D-aspartate, *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *GABA-B* γ-Aminobutyric acid, Type B, *VGKC* voltage-gated potassium channel, *PLEDs* periodic lateralized epileptiform discharges

Technical Component

EMG is a method of recording motor unit potentials with extracellular electrodes. This study is typically performed after a nerve conduction study (NCS) has narrowed the clinical diagnosis and suggested muscles that may be pathologically involved. To perform an EMG, a needle electrode is inserted into the muscle of interest. See Fig. 3.1. The needle may have a reference electrode embedded within it (concentric needle) or a monopolar needle with a surface skin reference electrode can be used. The tip of the needle is the active recording electrode and a triphasic waveform is produced as the muscle action potential approaches, reaches, and leaves the recording electrode. The needle is connected to an EMG machine which records and amplifies the signal and provides a visual and auditory representation of the signal [54, 59].

To perform the test, a needle electrode is placed in the muscle and electrical activity is noted during the insertion. Insertional activity from initial needle insertion should be only a few hundred milliseconds in duration. Insertional activity can be classified as normal, decreased (seen in fibrotic muscle disease) or increased (seen in denervated muscle). Next, the muscle is evaluated while it is at rest for any spontaneous activity. All muscle fibers of a given motor unit will fire at the same time as action potentials are an all-or-none response. Damaged and denervated muscle fibers become unstable and no longer fire with the rest of their motor unit. These damaged fibers can fire spontaneously with no external stimuli, producing spontaneous activity. Fibrillation potentials and positive sharp waves are the most common findings when assessing for spontaneous activity, and typically signify active denervation [54, 59, 60]. The patient is then asked to perform mild voluntary contraction of the muscle to evaluate motor unit potentials. Motor unit action potentials (MUAP) have typical morphology and characteristics. The duration reflects the number of muscle fibers within the motor unit and is typically 5–15 ms from initial take-off to the return to baseline. The number of phases, or times the waveform crosses baseline, is typically 2–4 in normal MUAPs. Polyphasia can be seen in both neuropathic and myopathic disorders. The amplitude of a MUAP is typically 100 μV–2 mV, and reflects only the few fibers that are nearest to the needle. After the MUAP is assessed with mild voluntary contraction, the patient is asked to perform maximal voluntary contraction of the muscle in order to evaluate recruitment and interference. Normally with muscle contracture, motor units can increase muscle force by increasing the firing rate or by recruiting additional motor units to fire. Decreased recruitment occurs when there is a loss of MUAPs, typically through axonal loss or conduction block, where additional units cannot be recruited easily. In contrast, increased or early recruitment typically occurs with myopathic processes where the individual muscle fibers within a unit cannot produce enough force and require additional motor units to generate a small amount of force. Once all of these factors are evaluated, the needle is moved to another location to repeat the above maneuver. The needle electrode samples muscle motor unit potentials in close proximity to the location of needle insertion; thus, multiple sites must be examined to have a thorough sampling of an area of interest. Typically, sampling is done in at least four directions from any given puncture site and multiple puncture sites are selected in one or several muscles of interest [54, 59, 60].

NCS can be performed to evaluate both nerve compound motor action potentials (CMAP) and sensory nerve action potentials (SNAP). CMAPs are measured in millivolts

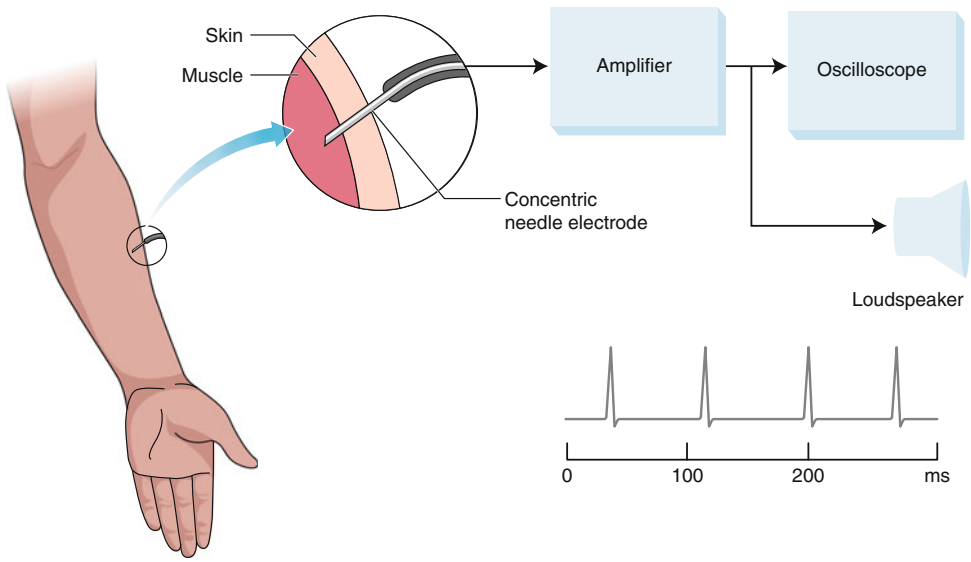

Fig. 3.1 Electromyography showing a needle insertion with EMG tracing

(mV) and are very large compared to SNAPs which are measured in microvolts (μV). While these have some differences in interpretation, much of the technical components remain the same [54, 59].

A stimulating probe is typically used with fixed surface electrodes that consist of a cathode (negative pole) and anode (positive pole) that are two to three centimeters apart. The cathode is positioned closer to the recording site. An electrical current is introduced into the stimulating probe. The current flows from the anode to the cathode, collecting negative charges between the cathode and the underlying nerve surface and depolarizing the underlying nerve. To record the stimulus for a motor nerve, an active recording surface electrode is placed over the belly of a muscle innervated by the nerve of interest, and a second inactive recording surface electrode is placed over the tendon of the muscle. When a stimulating current is given from the stimulating probe, the nerve is depolarized and the propagating muscle action potential is recorded at active recording electrode which is at the motor end point. See Fig. 3.2. Sensory nerves can be stimulated orthodromically (distal-to-proximal or in the direction of sensory flow) or antidromically (proximal-to-distal or opposite of the direction of sensory flow). Orthodromic recording is more commonly used; the active recording surface electrode is placed over the nerve and the second, inactive, recording surface electrode is placed at a remote site. Again, the stimulating probe depolarizes the nerve and propagates an action potential recorded at the given location on the sensory nerve [54, 59].

Several parameters are recorded and analyzed in a NCS. Amplitude (measured from baseline to the negative peak) reflects the number of muscle fibers that are depolarized. Duration (measured from the initial deflection from baseline to the first crossing of baseline) is a measure of synchrony of the muscle fibers. Conduction velocity (the distance traveled divided by the nerve conduction time) measures the speed of the fastest conducting axons. Latency (onset latency the time from the stimulus to the initial deflection from baseline), or peak latency (the time from the stimulus to the midpoint of the first negative peak) reflects the time from stimulation until a response is recorded at recording electrode. With motor studies, the distal motor latency includes the conduction time along the distal nerve, the neuromuscular junction (NMJ) transmission time, and the muscle depolarization time, necessitating two stimulation sites in order to subtract the time across the NMJ and muscle. With sensory studies, only one stimulation is needed to measure the latency and velocity [60].

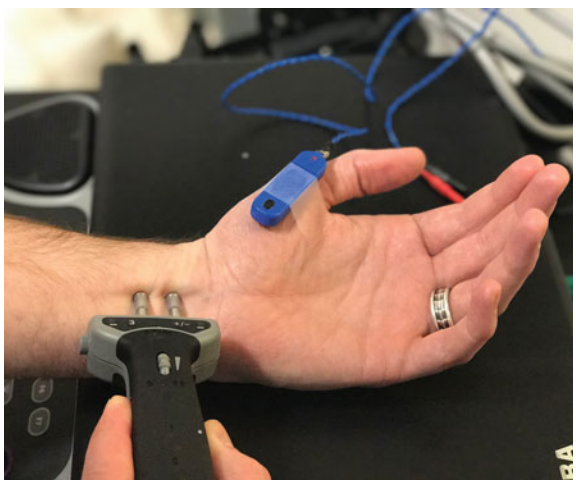

Fig. 3.2 Nerve conduction velocity. Depicting the stimulator with recording electrodes on the thenar eminence

There are several basic abnormal nerve conduction patterns. With neuropathic lesions one can see axonal loss, with reduced amplitude being the primary finding, or demyelination, with slowed velocity and latency. In myopathic disorders, the sensory NCS remain normal, as do the distal latencies and conduction velocities, with an occasional decrease in CMAP amplitude. These patterns are important in understanding etiologies of disease and correlating this with the clinical picture. See Table 3.4.

Indications and Contraindications

NCS and EMG are used to diagnose disorders of the peripheral nervous system (PNS), including disorders of primary motor neurons (anterior horn cells), sensory neurons (dorsal root ganglia), nerve roots, brachial and lumbosacral plexuses, peripheral nerves, neuromuscular junctions, and muscles. Patients with peripheral pain, paresthesias, sensory loss, atrophy, and weakness are routinely tested via EMG and NCS in order to better delineate an etiology and treatment plan. EMG and NCS have become a staple in our armamentarium and continue to provide useful diagnostic information in cancer patients.

At this time, there are no true contraindications of NCS. They are routinely performed in patients with pacemakers, cochlear implants, vagus nerve stimulators, deep brain stimulators, and other electric hardware as there are insufficient data to suggest significant risk to the patient [54, 59]. Although there is no clearly defined risk, a discussion with the patient's cardiologist may be advised if the NCS is to be performed close to the chest wall, or if dysfunction of the pacemaker may be life threatening [61, 62].

Patients with a bleeding tendency should be screened prior to performing routine EMG examination. The study maybe contraindicated in patients with untreated hemophilia or severe thrombocytopenia (typically considered platelets <20,000/mm [3]). Patients with iatrogenic blood thinning due to oral or intravenous anticoagulation should not

Table 3.4 Comparison of neuropathy versus myopathy

	NCV	CMAP	SNAP	MUAP
Neuropathy—axonal	Normal	Decreased	Decreased	Large
Neuropathy—demyelinating	Decreased	Normal	Normal	Normal
Myopathy	Normal	Decreased	Normal	Small

NCV nerve conduction velocity, *CMAP* compound muscle action potential, *SNAP* sensory nerve action potential, *MUAP* motor unit action potential

undergo EMG until there is some degree of reversal of the prothrombin time or partial thromboplastin time. In addition to bleeding tendency, EMG should not be performed in an area with local skin or soft tissue infection as there is a risk of bacteremia [54].

Local Cancer Invasion

Tumors can enter the peripheral nervous system by direct invasion or hematogenous spread. The tumor can then externally compress the nerve fibers or invade them. Neural compression is more common with many cancers causing local trauma to the nerve with resultant neurologic symptoms and deficits. Neural invasion is less common but has been demonstrated with prostate cancer, breast cancer, lung cancer, pancreatic cancer, and lymphoma [63].

Leptomeningeal metastasis or epidural tumors can cause radiculopathy with irritation or direct compression of the nerve roots. Plexopathies are quite frequent in approximately 1% of cancer patients with some metastatic involvement of their plexi [64]. Invasion of the lumbosacral plexus is more common and is often due to direct extension of abdominal and pelvic tumors including cervical cancer, colorectal cancer, bladder cancer, and retroperitoneal sarcomas. Invasion of the brachial plexus is typically due to breast and lung cancer. The lower trunk of the brachial plexus is most commonly involved due to its proximity to the lateral axillary lymph nodes [64]. Peripheral neuropathies are less frequent, but can be seen with peripheral nervous system infiltration from lymphoma called neurolymphomatosis. This is a well-known disorder and has been described with both B-cell and T-cell lymphomas [65]. It tends to invade multiple nerves or nerve roots and presents clinically as a polyneuropathy or polyradiculopathy [66]. Mononeuropathies are less common with local cancer invasion, but can occur with extension of bony metastasis. Malignant nerve sheath tumors that typically occur in the setting of neurofibromatosis I, or as a result of radiation therapy, can also cause a mononeuropathy [65].

The neurologic symptoms and deficits depend on the topography of the nerve involvement. Electrodiagnostic testing with EMG and NCS can be valuable in localizing nerve involvement to determine if the pathology is in the root, plexus, peripheral nerve, or neuromuscular junction. Although neurophysiologic testing does not distinguish local cancer invasion from other types of nerve damage, it can help localize the region of pathology so that a specific region can be imaged or biopsied for further investigation and prognostication.

Paraneoplastic and Antibody Mediated

Most paraneoplastic disorders begin acutely or subacutely and progress over time often with some stabilization late in the disease process. The current concept of paraneoplastic syndromes is that the primary tumor ectopically expresses an antigen that is identical in structure to a neural antigen but seen by the host immune system as foreign, thus eliciting an immune attack on both the antigen and the neural structure. The central nervous system or peripheral nervous system can be attacked, leaving the patient with debilitating symptoms. The incidence of paraneoplastic peripheral neuropathy is thought to be 6–8%, with most paraneoplastic neuropathies being sensorimotor and axonal [67]. Paraneoplastic disorders can also occur at the level of the neuromuscular junction or muscle. While antibodies and tissue pathology are more specific, EMG and NCS can be a valuable tool in the diagnosis of peripheral paraneoplastic disorders. Here we describe some common paraneoplastic and antibody-mediated disorders of the peripheral nervous system (motor neuron, nerve, NMJ and muscle) and their associated neurophysiologic findings. See Table 3.5.

Acute Inflammatory Demyelinating Polyneuropathy

An acute inflammatory demyelinating polyneuropathy (AIDP or Guillain–Barre syndrome) with acute to subacute weakness and sensory features has an increased incidence in patients with Hodgkin lymphoma as well as various types of solid cancers [68, 69]. With AIDP, typical findings include prolonged or absent F waves followed by increased distal latencies and conduction block of motor responses. Significant slowing of the motor nerve conduction velocities is not seen until later in the disease course. Sensory NCS can demonstrate absent or slowed conduction velocities. The needle EMG often remains normal or only with decreased recruitment [70].

Table 3.5 Autoantibody, paraneoplastic, and paraproteinemic diseases of the peripheral nervous system and associated EMG/NCV findings

	Associated cancer	NCV	EMG
AIDP	Hodgkin lymphoma, lung cancer, breast cancer	Prolonged F-wave	Normal or decreased recruitment
		Increased distal latencies	
		Conduction block	
CIDP	Lymphoma, leukemia, melanoma, paraproteinemia	Absent or prolonged F-wave	
		Increased distal latencies	
		Abnormal temporal dispersion, conduction block	
Paraproteinemic neuropathy	Amyloid, multiple myeloma, MGUS, Waldenström's macroglobulinemia	Decreased motor and sensory CMAP	Spontaneous activity an acute denervation
Anti-CV2	Small cell lung cancer	Decrease motor sensory CMAP	
Anti-Hu	Small cell lung cancer	Decreased sensory CMAP; Normal motor CMAP	Normal or active denervation
Mononeuritis multiplex	Vasculitic neuropathy, small cell lung cancer, uterine cancer, lymphoma, prostate cancer	Decreased sensory CMAP	
Neuromyotonia	Thymoma, lymphoma, small cell lung cancer		Spontaneous irregular firing of single or MUAP
			Persist during sleep and general anesthesia
Stiff person syndrome	Breast cancer, small cell lung cancer, Hodgkin lymphoma, colon cancer		Sustained continuous MUAP, disappeared during sleep and general anesthesia
Lambert-Eaton myasthenic syndrome	Small cell lung cancer	Decrement with slow rate repetitive nerve stimulation; 3–5 Hz	Single-fiber EMG-increased jitter
		High rate stimulation; 20–50 Hz results in increased CMAP	
Myasthenia gravis	Thymoma, lymphoma	Slow rate repetitive nerve stem; 3–5 Hz decrement in CMAP amplitude	Single-fiber EMG-increased jitter
		High rate stimulation-no increment	

AIDP acute inflammatory demyelinating polyneuropathy; *CIDP* chronic inflammatory demyelinating polyneuropathy; *CMAP* compound muscle action potential; *EMG* electromyography; *MUAP* motor unit action potential

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) has been reported in patients with solid and liquid tumors including adenocarcinomas, melanoma, and paraproteinemias [71, 72]. Clinically, these patients have slowly progressive sensory changes with large fiber sensory modalities being most affected. CIDP is distinguished from AIDP on the basis of a prolonged and relapsing course, enlargement of nerves, and responsiveness to

corticosteroids. Progression tends to be in a length-dependent manner for the sensory changes. The motor abnormalities are typically not as pronounced but are frequently present. The neuropathy may precede the discovery of the neoplasm. Similar to what is seen with acute inflammatory demyelinating polyneuropathy, the electrophysiologic studies demonstrate prolonged or absent F waves, increased distal latencies, abnormal temporal dispersion, and conduction block of motor responses [73].

Paraproteinemic Neuropathies

The prevalence of peripheral neuropathy is ten times higher in patients with paraproteinemias than it is in the general population. Peripheral neuropathy can occur with primary amyloidosis, multiple myeloma, monoclonal gammopathy of unknown significance, Waldenstrom macroglobulinemia, and other rare conditions. Paraproteinemic neuropathies are a heterogeneous group of disorders but with a great degree of overlap.

Patients with primary amyloidosis of the light chain type can develop a devastating peripheral neuropathy. The neuropathy consists of distal and symmetric progressive sensorimotor and autonomic dysfunction. The sensory symptoms are often small fiber predominant with persistent pain. Nerve conduction studies demonstrate decreased amplitude and, at times, mild slowing of conduction velocity consistent with axonal degeneration due to invasion of the nerves by amyloid. EMG can demonstrate increased spontaneous activity and evidence of acute denervation [67, 74].

Peripheral neuropathy can occur in multiple myeloma (MM) in several settings. With typical osteolytic MM, patients can have a mild sensorimotor axonal neuropathy with decreased motor and sensory amplitudes or a purely sensory axonal neuropathy with only sensory involvement. A demyelinating type of primary motor neuropathy can also be seen and resembles AIDP or CIDP as described above. Patients with MM associated with systemic amyloidosis can have prominent pain and small fiber sensory findings with electrophysiologic findings as seen in primary amyloidosis. Patients with atypical osteosclerotic myeloma tend to be younger and less ill. The neuropathy associated with osteosclerotic myeloma is chronic in nature with distal and symmetric sensorimotor changes. This neuropathy also resembles CIDP with a motor predominance and marked slowing in conduction velocities. These patients can develop a clinical syndrome (POEMS syndrome) with organomegaly, endocrinopathy, and skin changes [67, 74].

Patients with monoclonal gammopathy of unknown significance (MGUS) typically present with distal and symmetric chronic and progressive sensorimotor symptoms. Electrophysiologically, the peripheral neuropathy resembles a chronic inflammatory demyelinating polyneuropathy with slow motor nerve conduction velocities and increased distal latencies on NCS. Some MGUS patients have circulating anti-myelin-associated protein (anti-MAG) antibodies directed against peripheral nerve myelin. The majority of patients with anti-MAG antibodies have IgM-kappa monoclonal proteins in their serum [67, 74, 75].

Patients with Waldenstrom macroglobulinemia (WM) can develop symmetric and distal sensorimotor changes and a primarily demyelinating sensorimotor polyneuropathy on electrophysiologic testing. Similar to MGUS, some WM patients have circulating anti-MAG antibodies damaging the myelin and causing increased distal latency and slowed conduction velocity in motor and sensory nerves. Occasionally, WM is associated with an axonal pattern of neuropathy [67, 74, 75].

Anti-CV2

Anti-CV2 antibodies are seen in association with small cell lung cancer and can cause a variety of nervous system maladies including cerebellar degeneration, peripheral neuropathy, and uveitis. In up to 20% of patients, the anti-Hu antibody is also expressed. Patients with anti-CV2 typically have symmetric distal length-dependent sensory loss in all modalities with concomitant motor weakness. Electrophysiologically, a sensory motor axonal polyneuropathy is seen, but at times there are some demyelinating features. NCS demonstrates decreased amplitude of sensory and motor responses with some decrease in velocity of these responses [76].

Anti-Hu

Anti-Hu antibodies are now recognized as a common cause of paraneoplastic neuronopathy that affects the dorsal root ganglia. It is most commonly associated with small cell lung cancer, but is also present with other malignancies. The onset is typically rapid and painful but, unlike classic peripheral neuropathies, this neuronopathy can be asymmetric or non-length dependent in some patients. All sensory modalities can be affected, but the proprioceptive loss can be so profound that patients can have debilitating sensory ataxia. Anti-Hu was once thought to be only a sensory disorder, but evidence shows that some patients have a mixed sensorimotor picture [77, 78]. Electrophysiologic studies demonstrate axonal degeneration with low amplitude or absent sensory action potentials and preserved or abnormal motor responses on NCS. EMG is typically normal but, at times, can show signs of active denervation including fibrillation potentials and positive sharp waves [77, 79].

Mononeuritis Multiplex

A vasculitic neuropathy can be seen in association with malignancies. Vasculitic neuropathies typically present as mononeuritis multiplex, most commonly with asymmetric and patchy changes in sensory and/or motor nerves. The

symptoms can occur acutely or chronically, and are commonly seen with solid tumors, including small cell lung cancer, prostate cancer, uterine cancer, and lymphomas [67, 80]. Anti-Hu antibodies are sometimes associated with this disorder. On NCS, a primarily axonal neuropathy is seen with low amplitude sensory and compound muscle action potentials with minimal reduction of conduction velocities [79, 81].

Neuromyotonia

Neuromyotonia is a disorder characterized by peripheral nerve hyperexcitability due to spontaneous firing of motor unit action potentials. Clinically, patients can present with slow relaxation of muscles, cramps, stiffness, or myokymia. It is thought to be autoimmune mediated and can be associated with voltage-gated potassium channel antibodies or amphiphysin antibodies [67, 82]. Thymoma is the most common cause of paraneoplastic neuromyotonia, which can also be seen with lymphoma and small cell lung cancer [83, 84]. On EMG there is spontaneous irregular firing of single or multiple motor units at a rate of 150–300 Hz that can persist even in sleep and under general anesthesia [67].

Stiff Person Syndrome

Stiff person syndrome is characterized by painful muscle stiffness and rigidity typically involving truncal musculature. It can be autoimmune in nature and most commonly associated with glutamic acid decarboxylase antibodies. The paraneoplastic version of the disorder can have glutamic acid decarboxylase antibodies or more commonly amphiphysin antibodies. Breast cancer, small cell lung cancer, Hodgkin disease, and colon cancer are commonly associated cancers with the paraneoplastic version. On EMG, there are sustained continuous motor unit action potentials that disappear during sleep and with general anesthesia [67, 85].

Lambert–Eaton Myasthenic Syndrome

Lambert–Eaton Myasthenic Syndrome (LEMS) is one of the most common paraneoplastic syndromes although it can also be autoimmune in nature. About one-half of patients with LEMS have an underlying malignancy, with small cell lung cancer being the most likely culprit. Patients with paraneoplastic LEMS have V/Q voltage-gated calcium channel antibodies that bind presynaptically at the cholinergic junction preventing entry of calcium into the terminal axon and inhibiting the release of acetylcholine [86]. Patients present with fatigue and muscle weakness that is typically more proximal and can improve with repeated use. With LEMS, the compound muscle action potential in hand muscles are small at baseline and increase dramatically after exercise. With repetitive nerve stimulation at a slow rate of 3–5 Hz, there is a decrement in the CMAP amplitude due to failure of the neuromuscular junctions. When stimulated at a higher rate of 20–50 Hz, this is overcome with increased release of calcium and there is an increase in the CMAP amplitude. An increase greater than 100% in most muscles tested is suggestive of LEMS. Single-fiber EMG (SFEMG) can also be performed to help establish the diagnosis. With SFEMG, the variability in the timing of discharges of fibers is compared and an increase in this timing, known as jitter, demonstrates the insecurity of the neuromuscular junction [67, 87].

Myasthenia Gravis

In contrast to LEMS, myasthenia gravis (MG) is not considered a classic paraneoplastic syndrome because only a small portion of patients with the disease harbor a malignancy. Thymoma and lymphoma are the most common malignancies associated with the disease. When present, acetylcholine antibodies can aid in the diagnosis of MG but the antibodies do not distinguish paraneoplastic from non-paraneoplastic forms of MG. Clinically, patients have weakness in frequently used muscles and the weakness progresses throughout the day. Similar to LEMS, with repetitive nerve stimulation at a slow rate of 3–5 Hz, there is a decrement in the CMAP amplitude due to failure of the neuromuscular junctions. However, there is no increment with faster stimulation as seen with LEMS. Increased jitter is also seen with MG, again demonstrating the insecurity of the neuromuscular junction [67, 87].

Myopathies

Inflammatory Myopathy

Of the inflammatory myopathies, dermatomyositis (DM) and polymyositis (PM) have a clear relation to malignancy while this relationship is less clear with inclusion body myositis (IBM). DM and PM are associated with a wide range of cancers with lung cancer, ovarian cancer, and non-Hodgkin lymphoma being the most common [88]. With both DM and PM, patients have proximal symmetric weakness that typically evolves over weeks to months; muscle tenderness and pain are associated with this weakness. While muscle biopsy provides the definitive diagnosis, EMG can be a valuable tool in diagnosing inflammatory myopathies. With DM and PM, the EMG demonstrates a myopathic pattern with small amplitude short duration muscle potentials with early recruitment. Later in the disease, fibrillation potentials and positive sharp waves can be seen [67].

Necrotizing Myopathy

Necrotizing myopathy is a rare disorder that has been shown to have an association with gastrointestinal adenocarcinoma, transitional cell carcinoma, prostatic carcinoma, and non-small cell carcinoma. Patients have a rapid and progressive syndrome with symmetric proximal weakness and

pain. EMG studies in patients with necrotizing myopathy demonstrate abnormal spontaneous activity and decreased amplitude and duration of the motor unit potentials [89, 90].

Therapy-Induced Pathology

Chemotherapy Induced Pathology

Peripheral neuropathy is a common side effect of multiple chemotherapeutic agents. The taxanes, vinca alkaloids, and platinum compounds are the most notorious classes of agents that produce neuropathic side effects, but other less commonly known agents can be neuropathic as well. There are several patterns of disease caused by these drugs. While many cause diffuse polyneuropathies, some can cause myositis while sparing the peripheral nerves. EMG and NCS findings can be useful in diagnosing and following the recovery of these pathologic changes. Table 3.6 lists electromyographic findings associated with some common cancer treatments [91–97].

Radiation-Induced Pathology

Radiation therapy (RT) is frequently used as adjunctive treatment for malignancy. RT causes damage to both normal and abnormal cells often leaving unwanted side effects. Ionizing radiation causes cellular damage by breaking DNA, damaging RNA, proteins, and lipids, and by stimulating apoptosis [63]. Classically, there are three stages of radiation damage: acute (during the actual course of radiation), early-delayed (within weeks), or late-delayed (within months to years). While the acute and early-delayed stages are often reversible, the late-delayed stage is often chronic and can be progressive with few treatment options. The peripheral nervous system is more resistant than the central nervous system to the adverse side effects of radiation therapy, but despite this, peripheral nerve damage is a frequent complication of RT. The major sites of damage include the brachial plexus (typically after lymphoma, breast, or lung cancer treatment) and the lumbosacral plexus (after pelvic and abdominal treatment for numerous cancers) [63]. Distinguishing local cancer recurrence from radiation-induced plexopathy can be difficult. The clinical picture remains very important as several clinical factors aid in determining the diagnosis. With radiation-induced plexopathy, electromyography and nerve conduction studies can also be useful.

Myokymia on EMG examination may be the single most helpful electrodiagnostic finding in differentiating local cancer recurrence versus radiation-induced plexopathy [59, 98, 99]. Myokymic discharges are caused by the same motor unit and are groups of rhythmic spontaneous repetitive discharges (grouped fasciculations). With myokymia, the firing frequency is typically 5–60 Hz and the firing frequency between bursts is much slower. Myokymic discharges are likely due to spontaneous depolarization along demyelinated nerve segments. Clinically, myokymia looks like continuous involuntary rippling movement of a muscle [59]. Other EMG abnormalities are often seen in patients with radiation-induced injury. Fibrillation potentials, decreased motor unit potential amplitude, and increased motor unit potential duration are frequent findings associated with radiation injury but are nonspecific [99].

NCS abnormalities are also seen in patients with radiation plexopathy. These are not specific and can also be seen with direct neoplastic invasion. One such finding is conduction block due to an acquired demyelinating process. Conduction block is defined as a drop in compound motor action potentials amplitude of at least 20% between proximal and distal stimulation sites. Conduction block is frequently present in early-delayed and late-delayed radiation injury, but at times can also be seen with local neoplastic invasion. Sensory nerve conduction studies can have decreased amplitudes or be absent in patients with radiation injury [59, 98]. While NCS sensory changes are present in local neoplastic invasion, the incidence of abnormal NCS studies is greater in patients with radiation-induced injury [98].

Lumbar Puncture

History

The presence of fluid surrounding the brain was known for centuries. It was described by Hippocrates in the fourth-century B.C., Galen in the second-century A.D., and Valsalva in the 1600s [100]. In 1764, Contungo described fluid within the ventricles and subarachnoid space of 20 adults on whom he did lumbar taps [101]. Later in 1825, Magendie described tapping the cisterna magna in animals and postulated that there was continuity of the subarachnoid space around the brain and spinal cord. However, it was Axel Key and Magnus Retzius in 1875 who discovered what we know about cisternal anatomy today [102]. Soon after, Quincke developed a procedure using a percutaneous needle with a stylet to investigate hydrocephalus and tuberculous meningitis. He recorded the opening pressure with a manometer and was the first to study cell counts, protein, and glucose within the cerebrospinal fluid [103]. Nearly 50 years later, Merritt and Fremont-Smith published nearly 20 years of experience with cerebrospinal fluid studies at Boston City Hospital, providing a valuable reference point [104]. In the past century, the field has further advanced with radioisotopes, polymerase chain reaction (PCR), cytology,

Table 3.6 Cancer treatments and their associated EMG findings

Drug class	Drug names	Common uses	Mechanism of action	Clinical findings	EMG findings	NCS FINDINGS
Vinca alkaloids	Vincristine, vinblastine, vindesine, vinorelbine	Leukemia, lymphoma	Binds intracellular tubulin and inhibits polymerization	Symmetric distal sensory changes ±motor symptoms	EMG: rarely pathologic spontaneous activity in distal muscles	NCS: Axonal neuropathy with reduced amplitude of sensory > motor compound action potentials with late demyelinating features
				Autonomic neuropathy is common. "Coasting" phenomenon—worsening of symptoms despite withdrawal of agent		
Taxanes	Paclitaxel, docetaxel, abraxane, tesetaxel	Breast, ovarian, prostate, bladder, esophageal, head and neck cancers	Microtubule stabilizing agent that interferes with mitotic spindles during mitosis	Symmetric or asymmetric distal sensory changes, mixed small and large fiber	EMG: pathologic spontaneous activity in distal muscles, rarely myopathic changes on EMG	NCS: Axonal neuropathy with reduced amplitude and relative sparing of velocity of sensory > motor compound action potentials
				Motor symptoms are uncommon and mild but can include foot drop		
Platinum compounds	Cisplatin, carboplatin, oxaliplatin	Ovarian, bladder, testicular, lung cancers	DNA is damaged by intrastrand and interstrand crosslinks which induces apoptosis	Symmetric distal sensory changes—primarily large fiber modalities affected. Motor symptoms are extremely rare. "coasting" phenomenon with worsening of symptoms despite withdrawal of agent	EMG: no changes	NCS: Axonal neuropathy with reduced amplitude of sensory compound action potentials with late demyelinating features
Polysulfonated urea	Suramin	Prostate cancer	Inhibits reverse transcriptase	Symmetric distal sensory changes—mixed small and large fiber modalities. Motor symptoms are common but mild	EMG: rarely pathologic spontaneous activity in distal muscles	NCS: Axonal neuropathy with reduced amplitude of sensory and motor compound action potentials
				Guillian-Barre-like syndrome with severe, rapid predominantly motor demyelinating neuropathy can be seen, albeit rare	With the Guillian-Barre-like syndrome there is prolongation of F-wave latencies, decreased sensory and motor compound action potential amplitude and velocities, and temporal dispersion	
Angiogenesis inhibitors	Thalidomide	Myeloma, lymphoma	Inhibits angiogenesis	Symmetric sensory changes—mixed small and large fiber modalities affected. Motor symptoms are uncommon but mild	EMG: rarely pathologic spontaneous activity in distal muscles	NCS: Axonal neuropathy with reduced amplitude of sensory > motor compound action potentials

(continued)

Table 3.6 (continued)

Drug class	Drug names	Common uses	Mechanism of action	Clinical findings	EMG findings	NCS FINDINGS
Proteasome inhibitors	Bortezomib	Myeloma, lymphoma	Breakdown of intracellular molecules	Symmetric sensory changes with small > large fiber modalities affected	EMG: no changes	NCS: Axonal neuropathy with reduced amplitude of sensory compound action potentials
Monoclonal antibody	Ipilimumab	Melanoma	Targets human cytotoxic T-lymphocyte-associated antigen	Symmetric distal sensory changes. Motor symptoms can be seen	EMG: no changes	NCS: Sensorimotor polyneuropathy with demyelinating features with decreased amplitude and conduction velocities with conduction block
Nucleoside analogs	Gemcitabine	Pancreatic cancer	Replaces cytidine in DNA replication causing faulty DNA and apoptosis	Painful, symmetric, mild proximal weakness	EMG: motor unit action potentials with small amplitude, short duration, and early recruitment consistent with myopathic changes	

and other assays leading to widespread use of lumbar puncture as an essential tool for the diagnosis of many neurologic conditions [102].

Technical Component

A lumbar puncture is best performed with the patient in the lateral recumbent position with the craniospinal axis parallel to the floor and the patient in the fetal position with the head, knees, and torso flexed. The most superior part of the iliac crest is palpated and correlates with the L4 vertebral body at midline. Under sterile conditions and after local anesthesia, the spinal needle is advanced at the L3/L4 or L4/L5 vertebral interspace, angling slightly towards the head. Once the subarachnoid space is reached, the patient extends legs and a manometer is placed on the hub of the spinal needle to measure opening pressure. After pressure is measured, cerebrospinal fluid (CSF) is drained into sterile tubes. A total of 5–15 mL of fluid is typically collected during a routine lumbar puncture. However, in the workup of neurologic malignancy, more CSF may increase the yield and at least 10 mL should be collected for cytologic evaluation [102, 105, 106]. Fluoroscopic-guided lumbar puncture may be required if traditional lumbar puncture is failed at the bedside. If lumbar puncture is not possible, then cisternal puncture or cervical puncture may be considered. In modern day, these are done under fluoroscopy.

Indications and Contraindications

Lumbar puncture is useful in the diagnosis of many neurologic conditions including but not limited to: bacterial meningitis, viral meningitis, fungal meningitis, mycobacterial meningitis, vasculitis, subarachnoid hemorrhage, normal pressure hydrocephalus, central demyelinating disease, Guillain–Barre syndrome, central nervous system malignancy, carcinomatous meningitis, autoimmune encephalitis, and paraneoplastic encephalitis. The diagnostic role of lumbar puncture in neurologic malignancies will be discussed below.

There are several relative contraindications to lumbar puncture. Performing a lumbar puncture in a patient with preexisting increased intracranial pressure can precipitate deleterious consequences. Herniation syndromes can arise and can be life threatening. When increased intracranial pressure is suspected, computed tomography (CT) or magnetic resonance imaging (MRI) should be performed first to help assess the risk of herniation associated with lumbar puncture. Lumbar puncture in a patient with a focal mass with midline shift increases the risk of herniation and should be avoided [107].

Local skin infection, spinal epidural abscess, and epidural or vertebral malignancy in the lumbar region near the entry zone of the spinal needle is another relative contraindication. Performing a lumbar puncture through an infection, abscess, or malignancy can seed the CSF, increasing morbidity and mortality [102, 108].

Thrombocytopenia and anticoagulation also pose a risk when performing a lumbar puncture. It is generally advised to withhold lumbar puncture in patients who are actively bleeding, have platelets <50,000/μl, or an international normalized ratio (INR) >1.4. Aspirin and subcutaneous heparin at doses appropriate for deep vein thrombosis prophylaxis are not believed to pose a substantial risk [109–111]. Cisternal puncture is contraindicated in patients with an Arnold–Chiari malformation or posterior fossa tumor.

Composition of Cerebrospinal Fluid

CSF pressure is balanced carefully by the production from the choroid plexus and absorption from arachnoid granulations. Normal CSF opening pressure with a manometer while the patient is lying flat with legs extended is between 60 and 250 mm H_2O [112].

CSF is normal, clear, and colorless. Turbidity is rated from 0 to 4+ by most laboratories. Color is pathologic and can be due to infection, inflammation, or blood product. Three major pigments derived from red blood cells can be detected in CSF: oxyhemoglobin, bilirubin, and methemoglobin. Oxyhemoglobin is derived from lysed red blood cells and present in CSF by 2 h, peaks at 36 h, and typically disappears by 7 days. Bilirubin is first detected in CSF at about 10 h, reaches maximum in 48 h, and can persist up to 2–4 weeks after extensive bleeding. Oxyhemoglobin, and more so bilirubin, are the major pigments responsible for xanthochromia seen with subarachnoid blood. CSF bilirubin can be elevated with liver disease causing xanthochromia that can falsely mimic that found with subarachnoid blood. Methemoglobin, the latest byproduct of blood, is found in encapsulated subdural hematomas and in old loculated intracerebral hemorrhages [102].

Protein is largely excluded from the CSF by the blood–CSF barrier. The protein level in normal CSF is 20–45 mg/dl. A high protein level is nonspecific and can be due to an array of etiologies including but not limited to tumor, infection, trauma, stroke, hemorrhage, vasculitis, and demyelinating disease [105].

CSF glucose level is maintained by facilitated transport and simple diffusion. Glucose in CSF is derived from plasma glucose and is typically two-thirds of the plasma level. Thus, high or low glucose level should be corrected for serum glucose in order to make a proper assessment [105].

Under normal conditions, CSF is acellular. CSF can contain up to 5 white blood cells (WBC) per mm [3] and/or 5 red blood cells (RBC) per mm [3] without being considered pathologic. A cell count greater than this should be investigated. Unfortunately, not all lumbar punctures go as planned and interpreting a traumatic tap is often necessary. Under normal conditions, there may be an increase of 1 WBC for every 700 RBC introduced into the CSF for a traumatic tap. If there is a significant anemia or leukocytosis, the following formula may be implemented: where WBC_{REAL} is the calculated WBC count of the CSF before the traumatic blood was added, WBC_{CSF} is the WBC count in the bloody spinal fluid, WBC_{SERUM} is the WBC count in the serum, RBC_{CSF} is the RBC count in the bloody spinal fluid, and RBC_{SERUM} is the RBC count in the serum [102].

$$WBC_{REAL} = WBC_{CSF} - (WBC_{SERUM} \times RBC_{CSF})/RBC_{SERUM}$$

Focal Mass and Leptomeningeal Involvement

Brain metastases are a common complication of cancer. The incidence is 9–17% although this number is thought to be low as the incidence of brain metastases is increasing [113]. This increase in incidence may be due, at least in part, to improved imaging techniques. Additionally, the incidence may be increasing as we provide systemic treatments that prolong life, allowing the cancer to disseminate to the brain [114]. Breast cancer, lung cancer, and melanoma are the leading cancers with brain metastasis, and account for over two-thirds of all metastases [113].

Leptomeningeal metastasis is diagnosed in nearly 5% of patients with cancer metastasis. Again, this number is thought to be low as it is found to be much higher at autopsy [115]. The largest risk factor for leptomeningeal metastasis is the presence of parenchymal brain metastasis [116]. Additionally, primary brain tumors including astrocytomas, meduloblastomas, ependymomas, pineoblastomas, and oligodendrogliomas can infiltrate the CSF [117].

With solid tumor invasion of the brain (primary brain tumors and parenchymal metastasis), the CSF typically has a normal cell count, although there can occasionally be a pleocytosis that is most commonly seen with tumors near the ventricular surface or with large infiltrating gliomas. There is often normal glucose but an elevated protein concentration. This is in contrast to leptomeningeal metastasis, which typically demonstrates a more profound pleocytosis (approximately 50%), elevated protein (approximately 75%), and decreased glucose (approximately 30–50%) [102, 118]. The pleocytosis is typically due to lymphocytes, although eosinophilia can be seen with acute lymphoblastic leukemia and Hodgkin lymphoma [119]. Elevated opening pressure is often seen with leptomeningeal metastasis (nearly 50%) and large solid tumors [102, 118]. Although most patients do not have all of these features, completely normal CSF is uncommon [120].

Cytology

Positive cytology remains the gold standard for diagnosis of malignancy in the CSF. Unfortunately, despite having a high specificity, the sensitivity of cytology is between 50 and 90%. With parenchymal involvement alone the sensitivity is even lower [121, 122]. This often necessitates repeat lumbar punctures that can be difficult for both the patient and the physician. Several steps can improve the sensitivity of cytology: (1) A minimum of 10 ml of CSF should be submitted for cytology evaluation, (2) specimens should be fixed in ethanol-based fixative for cytology and should be processed immediately and not left overnight in the laboratory, (3) CSF should be obtained closest to the symptomatic site (lumbar puncture for spinal imaging or clinical findings and cisternal or ventricular puncture for cranial imaging or clinical findings). If these measures continue to provide negative cytology in the setting of clinical suspicion for parenchymal or leptomeningeal involvement, a second tap should be performed, again with the aforementioned measures in place. Although some perform further taps, little additional benefit has been shown for subsequent samplings [122]. Despite these efforts, CSF cytology remains negative in up to 20% of patients with clinical or radiographically unequivocal leptomeningeal carcinomatosis [116, 122]. It is important to note that sensitivity of cytology is reduced in primary CNS lymphoma with recent exposure to corticosteroids, which causes cytolysis [123]. A recent pilot study revealed the utility of rare cell capture technology in the diagnosis of leptomeningeal metastasis from solid tumor with 100% sensitivity and 97% specificity [124].

Flow Cytometry

Flow cytometry is a technique used to measure multiple characteristics of individual cells within a heterogenous population. Immunophenotyping can then be done to determine the composition of a group of cells by detecting cellular protein expression [125]. These methods are particularly useful in determining metastasis from hematologic malignancies. CSF flow cytometry can help identify whether atypical lymphoid cells lines are monoclonal or polyclonal [114, 126]. It can be used as an adjunct to CSF cytology to help increase diagnostic accuracy as almost 50% of patients have a positive flow cytometry in the absence of positive cytology [127]. With cytology and adjunctive flow cytometry, up to 80% of lymphoma cases with CSF involvement can be detected with the first CSF sample. Although rare, peripheral blood of a patient with active systemic lymphoma can contaminate the CSF causing false-positive CSF results. Thus, using CSF from a traumatic tap should be avoided when sending for flow cytometry [127, 128].

After flow cytometry is performed, CSF immunoglobulin heavy chain (IgH) rearrangement testing can be used to analyze the clonality of the antibodies being produced. Using PCR analysis of CSF, regions of the IgH can be amplified. In cases of neoplastic proliferation of lymphocytes, a unique arrangement is produced, resulting in a single sharp band on agarose gel. Conversely, nonneoplastic proliferation of lymphocytes, as seen with inflammatory processes, will reflect a widened band with multiple heavy chain sequences [128]. IgH rearrangement studies in the CSF for the detection of monoclonal antibody production have reported sensitivity of nearly 60% and specificity of nearly 85%. Similar to what is seen with cytology, recent corticosteroid treatment reduces the sensitivity of this study.

Biomarkers

Tumor markers in CSF can be useful when cytology is negative. The most usefulness is found with organ-specific tumor markers such as prostate-specific antigen (PSA-prostate), carcinoembryonic antigen (CEA-colon), carcinoma antigen 15-3 (CA 15-3-breast), carcinoma antigen 125 (CA 125-ovarian), carcinoma antigen 19-9 (CA 19-9-pancreatic), carcinoma antigen 72-4 (CA 72-4-gastric), melanoma antigen recognized by T cells (MART-1-melanoma), alpha fetoprotein (AFP-germ cell), and beta human chorionic gonadotropin (BhCG-germ cell). These can be relatively specific for leptomeningeal involvement when elevated in the CSF with the absence or markedly elevated serum levels [129–139].

Other novel biomarkers have been investigated but need more data in order to be useful clinically. Molecules involved in tumor invasion, angiogenesis, and metastasis (e.g., vascular endothelial growth factor, cathepsins, matrix malloproteinases, and lipid-associated sialic acid) show some promise, but are not sensitive enough at this time to improve cytologic diagnosis [139–145]. With vascular endothelial growth factor (VEGF), the sensitivities were 51.4–100% and specificities 71–100% [126, 140]. Levels of Beta2-microglobulin may be elevated up to 68% in leukemia or lymphoma with CSF involvement, but the false-positive rate was found to be as high as 25% [128]. Additionally, other biomarkers pertaining to brain metabolism have been studied but again with mixed results. In the brain, aerobic isozymes of LDH dominate (LD1 and LD2), reflecting the brain's dependence on aerobic metabolism. With malignant disease states, however, there is increased anaerobic LDH isozymes (LD4 and LD5). Patients with CNS malignancy were found to have higher LD5 anaerobic isozymes, with a 93% sensitivity. Unfortunately, LD5 elevation is also seen in bacterial meningitis and other conditions thus rendering this nonspecific [128, 146]. Proteomic analysis of CSF has

revealed several proteins that are differentially expressed in different tumor types. With CNS lymphoma there is some hope that a serine protease inhibitor, antithrombin III, may be useful clinically. Antithrombin III levels above 1.2 g/ml were able to detect CNS lymphoma with 75% sensitivity and 98% specificity [128, 140]. Further investigation of these biomarkers is necessary before they gain wide clinical use.

Paraneoplastic

Paraneoplastic neurologic syndromes are characterized by indolent tumor growth, inflammation of the nervous system, and immune activation against antigens shared by the tumor cell and the nervous system [147]. Paraneoplastic reactions can cause a wide array of neurologic syndromes encompassing the central nervous system and peripheral nervous system, including but not limited to limbic encephalitis, brainstem encephalitis, encephalomyelitis, cerebellar degeneration, and peripheral nerve disorders. Serum should be evaluated for suspected paraneoplastic neurologic syndromes but CSF studies for anti-Hu, anti-Yo, anti-Ma, anti-Ri, anti-CV2, and amphiphysin can be checked as well [148].

Abnormalities in the CSF can be found early on in paraneoplastic neurologic disease and can provide useful adjunctive information. In the vast majority of patients, the CSF is abnormal. Elevated white blood cells (>5 cells/mm [3]) are found in 47% of patients with lumbar punctures performed within one month of clinical symptom onset, but only 28% after the third month. Elevated protein (>50 mg/dl) is found in 71% of patients before the third month and only 61% after the third month. Oligoclonal bands are positive in over 60% of patients and remain stable over time. In up to 10% of patients, oligoclonal bands are the only abnormal finding in the CSF. Completely normal CSF is found in just 3% of patients with paraneoplastic neurologic syndromes with confirmed serum antibody when CSF is measured within the first month of clinical symptom onset [148].

Infections

Neurologic infections pose a serious risk to patients with cancer. Cancer patients are more susceptible to neuroinfectious disease for a number of reasons including cancer infiltrating the bone marrow, immunosuppressive therapies, radiation, neurosurgical procedures, indwelling ventricular catheters, and indwelling vascular catheters [149]. They are at increased risk of infection not only during the time of cancer treatment, but also before and after treatment. A few groups of cancer patients account for a large majority of those afflicted with neuroinfectious disease. Patients with lymphoma or leukemia represent one-fourth of the cancer population with CNS infection, while patients with primary brain tumors represent just over one-sixth of the population [150]. Patients with recent neurosurgery account for over three-fourths of cases of bacterial or fungal infection [151].

The organisms encountered in this population are diverse and differ from those in the general population. Additionally, in this population, two or more independent infectious agents can coexist. This is further complicated by the fact that up to one-third of neutropenic patients with culture positive bacterial or fungal meningitis can have normal CSF [151]. Adding to this complexity is the fact that cancer patients do not present with the classic symptoms of neurologic infection [149]. In fact, in one study only 5% of patients with culture positive meningitis presented with the triad of fever, nuchal rigidity, and mental status change, compared to 44% in the general population. Fever and headache were the most common isolated symptoms associated with meningitis in cancer patients [151]. Meningitis without focal signs is more typical in viruses, Candida, and Cryptococcus, while symptoms and focal deficits are more commonly seen in Toxoplasma gondii and Aspergillus [152]. Thus, lumbar puncture is an essential tool in the workup of infection or headache in patients with cancer even when clinical symptoms are scant.

Infectious patterns are important to recognize when trying to diagnose a suspected neurologic infection with CSF. In a

Table 3.7 CSF findings associated with abscesses, bacterial infections, fungal infections, and viral infections

	Normal	Abscess	Bacterial	Fungal	Viral
Pressure (mmH_2O)	60–250	Normal to elevated	Elevated	Normal to elevated	Normal
WBC count (mm^3)	0–5	Normal to elevated	>1000	10–500	10–500
Differential (Predominance)	None	Neutrophil	Neutrophil	Lymphocyte	Lymphocyte
Protein (mg/dl)	20–45	Normal to elevated	Elevated	Elevated	Normal to elevated
Glucose (mg/dl)	45–100 or >50% of serum	Normal	Low	Low	Normal

Table 3.8 Different immunodeficiencies and their associated infectious agents

Reason for infection	Infectious etiologies
Procedures: Craniotomy, Ventricular shunt, Ommaya reservoir, Intracerebral pressure monitoring devices, Central lines, Chemo ports, Feeding tubes	*Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli*, Enterobacteria, *Candida albicans*
T-lymphocyte deficit or dysfunction (Leukemia, Lymphoma, Hematopoietic stem cell transplantation, T-cell directed immunosuppressive therapies)	Human immunodeficiency virus, Cytomegalovirus, Herpes simplex virus, Epstein–Barr virus, *Cryptococcus neoformans*, *Candida albicans*, *Toxoplasma gondii*, *Listeria monocytogenes*
B-lymphocyte deficit or dysfunction (Paraproteinemias, Splenectomy, B-cell directed immunosuppressive therapies)	*Streptococcus pneumoniae*, *Haemophilus influenza*, *Klebsiella pneumonia*, Enteroviruses

clinical situation there are typically limitations to the quantity of CSF that can be obtained and the number of tests that can be sent for. Thus, narrowing the differential diagnosis in order to send the appropriate tests is important. Table 3.7 [102] lists CSF findings associated with abscesses, bacterial infections, fungal infections, and viral infections. Table 3.8 [150, 152] lists different immunodeficiencies and their associated infectious agents.

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