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Section 1 Differential Diagnosis of Abnormal Symptoms and Signs

Chapter 1

Introduction: localization and differential diagnosis in neurology

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Introduction

Generating a neurologic differential diagnosis can be very challenging. In contrast to many other fields of medicine, neurologic differential diagnosis requires the initial step of localizing abnormalities along the complex neuro-axis, before generating a list of potential etiologies. That step is predicated upon an appreciation of neuroanatomy and the associated symptoms and signs that apply to disturbances of specific parts of the neuro-axis. While numerous discussions may be found on this topic, often diffused among specific chapters in standard neurology texts, many students and even seasoned clinicians may be overwhelmed with the intricacies of neurologic localization. Some clinicians attempt to skip the logical thought processes involved in generating a differential diagnosis by immediately ordering numerous tests, hoping that the elusive explanatory lesion will demonstrate itself. This is unfortunate, since the most accurate diagnoses emerge from following a step-by-step approach which in turn guides the rational selection of specific tests.

The process of deriving a differential diagnosis can even precede the first face-to-face encounter between doctor and patient and truly begins with the clinician's receipt of any information about the patient. Even a requisition listing a reason for referral can lead to preparations for questioning that is relevant to generating a differential diagnosis. Rather than deferring the active thought process about possible localizations and causes until after the data from a generic history and examination are derived, proper procedure requires active consideration of localization and diagnostic possibilities from the very beginning. This process continues throughout the taking of the history and performance of the examination. The clinician should inquire about specific diagnostic hypotheses with answers to each query by the clinician, leading to further clarification achieved by issuing subsequent questions. The clinician should avoid focusing only on the early hypotheses about explanatory diagnoses and should keep an open mind about the diverse range of diagnostic possibilities. This book is designed to help with this process, providing descriptions of possible causes that can be integrated into the history and pursuit of abnormalities on examination that will support or discourage each diagnostic possibility.

The neurologic history

Information elicited through the history and examination is essential not only for localizing the abnormality but also for identifying possible etiologies. A focused history begins with clarification of the chief complaint. Patients' descriptions of their symptoms need to be clarified by the clinician as what is stated may not be equivalent to what is actually meant. For example, many patients will use the term numbness when they really mean weakness. A complaint of dizziness may actually mean gait unsteadiness.

Particularly crucial to generating a list of diagnostic possibilities is knowledge about the "whats, wheres, hows, etc." that give context to the symptom or sign, and are usually a part of the history of present illness (HPI) portion of the history.

For example [1]:

- When: When did the symptom begin? When did it stop? Did it recur? How often does it happen? How long does it last? Has it changed over time?
- What: What happens? (Step-by-step description is often helpful.) What do others see? What does it feel like? What brings it on? What makes it worse? What makes it better?

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- Where: Where on the body do the symptoms occur? Where does it radiate to? Where was the patient and what was the patient doing when the symptoms developed, what were the circumstances?
- How: How severe is it? How does it affect daily life?
- Why: What does the patient believe is causing the symptoms? What are their greatest fears about the symptoms?

Beyond these more generic questions, specific questions that relate to elements of the differential diagnosis should be asked to either support or discourage possibilities that could explain a symptom. These questions can be generated by referring to the differential diagnosis table included in each chapter of this book. For example, if a migraine headache is a possibility, the clinician may not only ask the generic question about what brings it on, but may also inquire about possible precipitants such as sleep deprivation or ingestion of wine, or other questions that specifically relate to migraine headaches. Active history-taking is a balancing act between guiding the patient to provide the relevant information and permitting the patient to provide the most spontaneous account without "leading the witness."

Past medical and psychiatric history provide a context in which symptoms occur. The patient with an established history of breast cancer who presents with progressive hemiparesis raises the concern about possible metastasis. Review of systems provides additional background information that may not be elicited on the more focused, earlier portions of history-taking. It also embraces the concept that concomitant illnesses may not only predispose the patient to neurologic disorders but also may be the result of or impacted by neurologic disease [2].

Family history may also provide important clues about diagnostic possibilities. A family history of a condition or specific genetic disorder may heighten suspicion of a distinct diagnosis, and may also lead to recommendations to examine other family members. Social history is replete with potentially invaluable clues to diagnostic possibilities. History of substance abuse, or stressors, may be very relevant toward symptoms.

The history should also go beyond the patient's own account of symptoms. Witnesses' accounts and review of prior records and prior diagnostic work-up can be invaluable.

The neurologic examination

Abnormalities along the neuro-axis are further clarified by seeking the presence or absence of findings on examination. While the examination is traditionally performed after a thorough history is obtained, in fact the experienced clinician begins the examination from the moment of the first encounter with each patient, observing a potential multitude of signs that will be evident in the way the patients present themselves. During the formal examination, the seasoned neurologist is able to identify and accurately classify examination findings such as movement abnormalities or what exceeds the normal variations in findings among different individuals. Performing a rote detailed neurologic examination for every patient irrespective of presenting symptoms is a suboptimal way of attaining relevant data and is frankly not feasible for the typical busy clinician. More desirable is a hypothesis-driven focused neurologic exam that is supplemented by a general screening neurologic exam to ensure that important additional findings have not been ignored.

Examination includes elements of the general examination that are relevant to neurologic disorders such as vital signs, neurocutaneous abnormalities, heart exam, presence or absence of bruits, etc. Abnormalities found on the neurologic examination should lead to hypotheses about localization that are supported or dismissed by symptoms on history and additional findings sought on examination. Validation of subtle abnormalities is supported by asking the patient to perform additional tasks that test similar function. Additional signs should also be sought that would make sense to be abnormal in the face of dysfunction of that portion of the neuro-axis.

Localizing abnormalities along the neuro-axis

The reader is directed to the diverse anatomical diagrams featured in each of the chapters of this book. As most symptoms or signs may be explained by deficits at different points of the neuro-axis, it is helpful to systematically consider the specific features of different neurologic sites. For example, unilateral paresis may arise from a problem in the cortex or as distal as the neuromuscular junction or muscle itself. What leads the neurologist to favor one localization over another is an understanding of what to expect with problems at each site along the neuro-axis.

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Neurologic localization of the deficit is made more complex by the fact that the origin of the disturbance may not necessarily be directly within the area where the deficit appears to come from. For example, deficits in one region may arise from compressive effects from an expanding mass, from cerebrospinal outflow problems, or poorly localized inflammatory or neurodegenerative processes of neurons or their axonal components [3]. For example, while most neurologic localization tends to be contralateral to a central nervous system (CNS) hemispheric lesion, compressive effects in transtentorial herniation can affect the contralateral cerebral peduncles causing hemiparesis ipsilateral to the side of a hemispheric mass lesion [4]. Localization is also challenging if the site of suspected disturbance cannot be adequately explained by one specific localization site and hence is deemed multifocal, or if the process represents a diffuse disturbance such as toxic–metabolic systemic effects [3].

The clinician takes each symptom and sign and considers its potential sites of localization. Then, applying principles of parsimony, the clinician considers among the diverse list of localization sites, a common area that could explain most or all symptoms or signs. Further evidence for the responsible site of localization can be sought by pursuing more queries in the history or performing specific examination maneuvers that support that site of localization.

One particularly challenging aspect of performing a history and examination occurs in the individual with a primary psychiatric disorder or when there is significant psychiatric comorbidity of neurologic disease. Active pursuit of higher integrative functions may be performed in individuals with memory complaints but it is also important to enquire about and look for signs of depression. Individuals with conversion disorder or malingerers may exhibit abnormal signs on examination and careful examination of potential inconsistencies and other classic functional signs such as Hoover's sign, non-physiologic visual fields, or one of many types of functional gait may be elicited. Clinicians should be especially careful to avoid misidentifying aphasia as psychotic thinking, or misattributing altered behavior due to diffuse or bilateral hemispheric lesions as merely part of a primary psychiatric disease.

While a comprehensive discussion of neuroanatomy is beyond the scope of this chapter, selective features of anatomical sites and anticipated findings are noted below. The typical neurologist will not compare the constellation of symptoms and signs of the individual patient against each and every possible localization site but rather begin with consideration of broad categories of neurologic localization. A typical starting point will be deciding between localization in the CNS versus peripheral nervous system (PNS). Longstanding CNS deficits may be associated with cognitive or language difficulties, visual field cuts, and upper motor neuron signs such as hyperreflexia and the Babinski sign. Problems in the PNS may feature muscular atrophy, fasciculations, and diminished reflexes [4]. If the lesion is focal and suspected to be within the CNS, the next question is whether the lesion is intra-axial or extra-axial. If intra-axial, major areas to be considered would include the cerebral hemisphere, ventricular pathways, basal ganglia, brainstem, cerebellum, or spinal cord. Extra-axial lesions should also be considered including those emanating from surrounding bone or the meningeal space such as epidural, subdural, or subarachnoid regions [5].

Lesions involving the cerebral hemispheres including the cerebral cortex

These localizations may be cortical, subcortical, or combinations. Hemispheric lesions that involve the pyramidal (corticospinal) tracts are evidenced by upper motor neuron injury signs including usually contralateral paresis, spasticity, increased deep tendon reflexes, and the Babinski sign. The corticospinal tract may be affected further down its long pathway and therefore other cerebral hemispheric signs help the clinician identify the localization in the cerebral hemispheres. Upper motor neuron injury is distinguished from peripheral nerve disturbances; the latter associated with weakness in the company of loss of tone and atrophy, diminished reflexes, and absence of the Babinski sign [6]. Hemisensory loss, hemifield visual field cuts, and partial seizures are other clues to hemispheric insults.

Many lesions of the cerebral cortex that show classic "cortical signs" are in fact often not restricted to the superficial cortex but also involve subcortical regions. A classic example is the large vessel territory stroke. Findings that suggest involvement of the cortex include higher-level deficits such as agnosia or apraxia syndromes. Aphasia may occur if the dominant hemisphere (usually left) is affected. Other

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dominant hemisphere syndromes depending on the site of disturbance include alexia without agraphia, and the Gerstmann syndrome. In the non-dominant hemisphere, more subtle signs including denial, neglect, and constructional apraxia are elicited by examination and less likely through taking the history alone. Cortical deficits associated with affectation of either hemisphere include the superimposition of "cortical sensory" deficits on top of primary modality sensory loss. Examples include problems in two-point discrimination, graphesthesia, and stereognosis. Dramatic syndromes such as the alien hand syndromes point to a cortical localization. While some "cranial nerve" deficits such as unilateral facial sensation loss may occur with cortical lesions, there is usually preservation of functions of cranial nerves II (pupillary response), VIII (hearing), along with IX, X, and XI. With cortical lesions, corticospinal fibers are less consolidated and therefore lesions are more likely to produce more variability in the severity of weakness in the face, upper and lower extremity.

With regard to lateralized deficits, it is useful to consider whether findings suggest a specific lobe or lobes, or specific vascular territories. The effects of deficits in specific lobes of the brain are highlighted in Table 1.1.

Alternative distributions that may affect portions of one lobe or involve more than one lobe of the brain include classic vascular territory lesions of the cerebral cortex and subcortical regions. For example, middle cerebral artery territory deficits which include subcortical regions classically produce contralateral deficits of arm and face more than leg, and contralateral sensory loss with increased reflexes. If originating in the dominant hemisphere, aphasia will be apparent. Other findings include apraxia, contralateral field deficits, and early on there may be gaze deviations to the side of the lesion. Anterior cerebral artery territory lesions cause deficits of contralateral leg more than arm and face. There may be contralateral cortical sensory loss in the leg, and increased deep tendon reflexes. Additionally, incontinence and frontal lobe signs may be present. Posterior cerebral artery territory deficits may produce a homonymous hemianopia, contralateral sensory loss, and sometimes visual agnosia or alexia without agraphia. Borderzone vascular territory syndromes termed watershed syndromes, such as the bilateral anterior watershed territory (man in a barrel syndrome) ischemic syndromes, can be particularly challenging to identify.

Box 1.1 Subcortical white matter disturbances.

Syndrome	Localization	Findings
Dysarthria clumsy hand syndrome	Junction internal capsule and corona radiata (also seen with pontine lesions)	Facial paresis, dysarthria, mild paresis and clumsiness of contralateral hand
Ataxic hemiparesis syndrome	Posterior limb of internal capsule, pons	Contralateral dysmetria and distal lower extremity paresis
Pure motor stroke	Corona radiata, genu or posterior limb of internal capsules. (Also seen with lesion in pons or medullary pyramids)	Contralateral paresis or plegia without sensory deficits, cortical signs or visual field deficits

Subcortical white matter disturbances

Consolidation of pyramidal tract fibers makes it feasible that even small lesions can produce substantial deficits (Box 1.1). While affectation of the corona radiata may elicit more variability in degree of paresis among face, arm, and leg, lesions of the posterior limb of the internal capsule may produce a uniform deficit throughout the contralateral side. Sufficiently large subcortical lesions often produce visual field deficits.

Examples of subcortical lesions include lacunar strokes.

Bilateral subcortical processes commonly connote demyelinating disease.

Subcortical gray matter lesions

Thalamic lesions should be considered in the face of profound contralateral primary modality sensory deficits. Many other thalamic-related symptoms have been reported depending upon the specific nucleus affected. These include contralateral severe pain, transcortical aphasia, or acute agitation.

Basal ganglia affectation should be considered with findings of Parkinsonian symptoms (e.g. pill-rolling resting tremor, bradykinesia, festinating gait, postural loss), hemiballismus, chorea, or athetoid movements. Patients may also complain of swallowing difficulties, and alterations of speech articulation and gait.

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Table 1.1 Localization of forebrain lesions.

Site	Finding
Left frontal lobe	Anterior aphasia (Broca's transcortical motor), aphemia Ideomotor apraxia Voluntary rightward saccades, left gaze preference Right hemiparesis, deep tendon reflex, and Babinski sign
Right frontal lobe	Motor neglect of left world Ideomotor apraxia Voluntary leftward saccades, right gaze preference Left hemiparesis, deep tendon reflex, and Babinski sign
Bilateral frontal lobes	Perseveration, impersistence, stimulus-bound responses Impaired executive functions: planning, sequencing, judgment, insight, abstract reasoning Impaired motor (Luria) sequencing Snout, root, grasp, and palmomental reflexes Gegenhalten (paratonic rigidity)
Orbitofrontal	Disinhibition, aggressive impulsivity Anosmia Memory disturbance
Frontal convexity	Abulia – akinetic mutism Incontinence "Magnetic" gait
Midline frontal	Bilateral leg weakness Behavioral changes (cingulate gyrus)
Left parietal lobe	Right cortical sensory loss (astereognosis, agraphesthesia, two-point discrimination) Anomic aphasia, transcortical sensory aphasia, dysgraphia, dyscalculia, left–right disorientation, finger agnosia Right inferior quadrantanopsia
Right parietal lobe	Left cortical sensory loss (as above) Left-sided neglect, anosognosia, asomatognosia Constructional apraxia, dressing apraxia Left inferior quadrantanopsia
Left temporal lobe	Posterior aphasia (Wernicke's, transcortical sensory) Conduction aphasia Amnesia for verbal material (usually bilateral lesions) Right superior quadrantanopsia
Right temporal lobe	Dysprosody, amusia, non-verbal auditory agnosia Amnesia for non-verbal material (usually bilateral lesions) Left superior quadrantanopsia
Bilateral temporal lobes, medial perisylvian	Amnesia Cortical deafness Auditory agnosia
Occipital lobe	Contralateral homonymous hemianopsia (macular sparing)
Left	Alexia without agraphia (requires lesion of splenium of corpus callosum)
Parieto-occipital	Balint syndrome (simultanagnosia, optic ataxia, ocular apraxia), impaired visuospatial localization
Temporo-occipital	Visual agnosias (including prosopagnosia, color agnosia, achromatopsia) Visual amnesia Confusional state

Modified from Table 1–1 in [7] with permission.

Diffuse or bilateral hemispheric disturbances

The category of diffuse cortical involvement may be applied to situations in which there is no clear-cut lateralization to findings. This may be associated with depressed mentation either with altered sensorium as in a toxic–metabolic encephalopathy or with preserved sensorium but altered cognition as in a dementia. Bilateral corticobulbar tract disturbances can produce a pseudobulbar palsy characterized by dysarthria, loss of inhibition of emotional expression, and hyperactive bulbar reflexes.

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Table 1.2 Localization of brainstem lesions.

Site	Finding
Midbrain tectum and pretectum	Parinaud syndrome (large pupils with near-light dissociation, convergence–retraction nystagmus, impaired upgaze, eyelid retraction)
Tegmentum	Abnormal pupils: midrange, unequal, irregularly shaped Impaired vertical eye movements Anterior INO Skew deviation Decreased arousal Nuclear CN III lesions (including bilateral ptosis and superior rectus deficits) Nuclear CN IV lesions (contralateral CN IV deficit)
Cerebral peduncles	Weber syndrome (ipsilateral CN III, contralateral hemiparesis)
Red nucleus	Benedikt's syndrome (ipsilateral CN III, contralateral tremor)
Ascending cerebellar fibers	Claude's syndrome (ipsilateral CN III, contralateral cerebellar ataxia)
Pons tegmentum	Ipsilateral gaze palsy ("wrong-way eyes") Internuclear ophthalmoplegia One-and-a-half syndrome Skew deviation CN V, VI, VII, and VIII lesions
Basis pontis	Contralateral hemiparesis Contralateral ataxia Dysarthria
Medulla lateral	Wallenberg syndrome (ipsilateral CN V, ipsilateral Horner's syndrome, contralateral loss of pain and temperature below the neck [spinothalamic tract], vertigo and ipsilateral nystagmus, ipsilateral CN IX and X deficits, skew deviation)
Medial	Ipsilateral CN XII deficit, contralateral hemiparesis, contralateral medial lemniscus deficit (joint position and vibration)

CN, cranial nerve: INO, internuclear ophthalmoplegia.
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Brainstem syndromes

Lesions of the brainstem are usually suspected when there are crossed deficits, usually with ipsilateral motor or sensory deficits on the face but contralateral deficits in the rest of the body, or in company with specific cranial nerve deficits such as those subserving eye movements, facial sensation, facial movements, or swallowing [4]. Depending on the site of brainstem involvement, patients may complain of varying combinations of double vision, speech articulation difficulties, vertigo, facial numbness, or facial weakness contralateral to limb weakness. The ocular motility disorder internuclear ophthalmoplegia (INO) indicates a disturbance of the medial longitudinal fasciculus in the brainstem.

Cerebellar syndromes

These are traditionally divided into the appendicular type referring to lateral cerebellar hemispheric problems and characterized by ipsilateral signs of ataxia including dysmetria and intention tremor, dysdiadochokinesia and diminished tone in the ipsilateral limbs. Truncal or midline cerebellar deficits are suggested by a wide-based gait, scanning speech, and truncal titubation. Affectation of the flocular-nodular lobe is associated with vestibulocerebellar ataxia characterized by many ocular findings including nystagmus, distortion of smooth and saccadic pursuits, ocular malalignment, diplopia, and oscillopsia, along with episodes of vertigo, gait and motor ataxia along with head tilting [8].

Spinal cord syndromes

These should be suspected when the face is spared and with motor and sensory deficits at levels below the lesion [4]. Sphincter dysfunction due to autonomic fiber involvement is another clue to spinal cord localization.

Lesions of the high cervical area are the exception to the facial sparing rule and should be considered in the presence of upper and lower extremity upper

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Table 1.3 Localization of spinal cord lesions.

Site	Finding
Spinal cord	Bilateral signs LMN signs at the level of the lesion UMN signs below the lesion Marked spasticity with Babinski signs Absent jaw jerk Sensory level at or below the level of the lesion
Craniocervical junction	Neck pain, head tilt Downbeating nystagmus UMN signs of all four extremities
Cervical spinal cord	Neck pain Root signs at the dermatomal level of the lesion in the neck, shoulders, or arms Long tract signs below the level of the lesion (usually bilateral) Sensory level at or below the level of the lesion Spastic bowel and bladder (later)
Thoracic spinal cord	Back pain Root signs at the level of the lesion Paraparesis: long tract signs below the level of involvement Sensory level below the level of involvement Spastic bowel and bladder
Conus medullaris (S3–Coc1)	Early bowel, bladder, and sexual dysfunction; usually areflexic (LMN) bladder outlet obstruction. Early perineal hypesthesia No motor signs in legs (if pure) Distal motor signs with loss of ankle jerks (if epiconus, L4–S2)
Cauda equina anterior cord syndrome	AHC (LMN) involvement at the level of the lesion Corticospinal tract involvement below the lesion Spinothalamic tract involvement below the lesion Sparing of the dorsal columns Spastic bowel and bladder
Central cord syndrome	Segmental loss of pain and temperature at the level of the lesion UMN signs below the lesion Sparing of dorsal column modalities Sacral sparing
Brown–Sequard (hemicord) syndrome	Ipsilateral corticospinal tract signs below the lesion Ipsilateral loss of vibration and joint position sense below the lesion Contralateral loss of pain and temperature below the lesion Band of ipsilateral hypesthesia to all modalities at the level of the lesion

AHC, anterior horn cell; LMN, lower motor neuron; UMN, upper motor neuron.
Reprinted with permission from [7].

motor neuron signs in the absence of hemispheric or brainstem deficit signs.

Pyramidal tract involvement is associated with upper motor neuron type deficits such as spasticity which may be perceived as stiffness in the lower extremities. Distal weakness tends to exceed proximal weakness. Classically, there is a sensory "level" representing a sharp line below which there is diminished sensation.

The nature of the deficits in spinal cord lesions depends not only upon the lesion localization in the rostro-caudal plane but also in the transverse plane, since there are many and diverse motor and sensory tracts running perpendicularly at different antero-postero and lateral regions along the transverse plane. Upon suspecting a myelopathic localization, the clinician should then consider specific spinal cord patterns. For example, a complete transverse cord syndrome of the thoracic cord will produce paresis of both lower extremities, a sensory level and sphincter problem. An anterior cord syndrome such as that due to anterior spinal artery insufficiency affects the lateral spinothalamic tracts and hence creates a sensory level for pain and temperature sensation but spares the dorsal columns that subserve joint position and vibration. A motor deficit may also occur.

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Table 1.4 Localization of lower motor neuron lesions.

Site	Finding
Anterior horn cells	Evolves to involve all four extremities (may not at first) – LMN involvement of the lower extremities may distinguish it from cervical spondylosis – in ALS Atrophy, fasciculations, and weakness Hypotonicity and loss of reflexes Tongue and other involvement above the neck (in ALS) Usually with associated UMN signs (in ALS)
Roots	Dermatomal pain and paresthesias Unilateral (unless multiple, as in GBS) Dermatomal sensory loss Myotomal weakness Isolated DTR
Cauda equina	Low back and perineal pain LMN deficits of the lower extremities (may be asymmetric) Early areflexic bladder and bowel
Nerve mononeuropathy	Pain and paresthesias in sensory nerve distribution (light touch loss typically involves greater area than pinprick loss) Sensory and motor deficit characteristic of a peripheral nerve
Polyneuropathy	Usually distally predominant stocking–glove distribution Deficit gradient from distal to proximal Symmetric deficits Loss of motor, sensory, or autonomic function, depending on the nerves involved Loss of ankle jerks in most

ALS, amyotrophic lateral sclerosis; DTR, deep tendon reflex; GBS, Guillain–Barré syndrome; LMN, lower motor neuron; UMN, upper motor neuron.
Reprinted with permission from [7].

Posterior column syndromes, such as with tabes dorsalis or vitamin B12 deficiency, spare pain and temperature but create joint position and vibration sensory loss. The hemicord Brown–Séquard syndrome causes ipsilateral paresis due to affectation of lateral corticospinal tracts and anterior horn cells, and ipsilateral pain and temperature of only one segment due to effects on the nerve root entering the cord and crossing to the contralateral spinothalamic tract. Contralaterally, there is pain and temperature deficit below the affected level.

A "suspended" sensory level may occur with involvement of inner laminations of the spinothalamic tract and crossing fibers traveling to each spinothalamic tract and creating pain and temperature sensory deficits in a cape, unilateral limb, or in multiple adjacent segments.

Affectation of the anterior horn cell region spares upper motor neurons and creates muscle atrophy, flaccid paresis, and diminished deep tendon reflexes.

Another classically cited distinction is made between lesions that are intramedullary (where dissociation of pain and temperature deficits from joint position and vibration is more common) and extramedullary (upper motor neuron signs tend to occur later, radicular pain is less likely, and sphincter loss is more common). Extramedullary lesions are further classified as extra- or intradural.

The lowest spinal cord lesions, involving the conus medullaris (associated with lower sacral root sensory loss – perianal hypesthesia, less intense radicular pain, and L5–S1 motor deficits such as ankle paresis) are distinguished from the cauda equina syndrome characterized by saddle hypesthesia, lower motor often asymmetric paraparesis, multiple sensory dermatomal loss, later sphincteric dysfunction, and marked radicular pain [9].

Lower motor neuron syndromes

Dorsal root ganglion

Sensory neuronopathies may be confused with sensory polyneuropathies. Sensory neuronopathies are characterized by profoundly diminished vibration and proprioceptive loss, profound sensory ataxia, and loss of reflexes that may be worse in hands compared with feet. Pain and temperature modalities are less affected.

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Nerve root

This is suggested by the finding of specific dermatomal sensory loss and myotomal deficits that fit the distribution of a nerve root. Radiating pain often in association with neck or back pain is common.

Plexus

A plexus lesion should be suspected when sensory motor deficits suggest a distribution that goes beyond a single nerve. Classic types of brachial plexopathies include the Erb–Duchenne upper trunk C5–C6 plexopathy where the upper extremity assumes a dangling limp extended posture. There are many other varieties of complete or partial brachial or lumbosacral plexopathies.

Specific nerves

Mononeuropathies are suspected when motor and sensory deficits fit within the distribution of a single nerve. Specific examples of mononeuropathies are highlighted in specific chapters of this book. Some mononeuropathies involve nerves consisting of primary sensory fibers and hence produce sensory deficits such as on the thigh seen with meralgia paresthetica due to problems of the lateral femoral cutaneous nerve.

Mononeuropathy multiplex is characterized by involvement of multiple nerves, often in random areas. Over time, progressive involvement of more nerves and increased severity of deficits lead to the potential confusion with polyneuropathies.

Peripheral neuropathies

Generalized neuropathies are associated with usually distal sensory loss (classically a "stocking–glove distribution"), distal paresis, atrophy, fasciculations, and diminished reflexes. Classic neuropathies are length dependent and typically begin in distal extremities and climb more proximally. The many varieties of polyneuropathies, such as those that are predominantly sensory or predominantly motor, are discussed in detail in the chapter on this topic.

Syndromes with combined upper and lower motor neuron deficits

This combination, summarized under the term "motor neuron disease," is the hallmark of amyotrophic lateral sclerosis (ALS) and is distinguished from pure upper motor neuron diseases such as primary lateral sclerosis and purely lower motor neuron disease such as the spinal muscular atrophies. Motor neuron disease displays combinations of upper motor neuron deficit signs such as spasticity and hyperreflexia with lower motor neuron deficit signs such as muscle atrophy and fasciculations. Progressive diffuse weakness, along with speech, swallowing, and respiratory difficulties occur in ALS.

Motor neuron disease should be distinguished from cervical lesions such as spondylosis or neoplasms in which there are lower motor neuron signs in the upper extremities due to nerve root compression but myelopathic upper motor neuron signs such as spasticity evident in the lower extremities.

Syndromes with combined spinal cord and peripheral nerve lesions

Subacute combined degeneration associated with vitamin B12 deficiency is an example where the problem involves two sites of the neuro-axis. Peripheral neuropathy is an often painful sensory or sensorimotor neuropathy while affectation of the lateral and dorsal columns of the spinal cord produces severe proprioceptive sensory deficits along with spasticity and paraparesis. Involvement of other sites in the nervous system can lead to other symptoms such as dementia or visual deficits.

Neuromuscular junction

This is often suspected in the presence of fluctuating weakness, usually with exacerbation with use of the affected musculature (unless a Lambert–Eaton variant), and typically improving with rest. Sensory loss is absent. Examination often documents fatiguability usually of proximal muscle groups and often includes facial, especially ocular, musculature. Bulbar musculature involved in the neuromuscular junction (NMJ) syndrome of botulism can be confused with brainstem lesions such as stroke which will present more static classic combinations of findings that fit with specific vascular syndromes. Acute inflammatory demyelinating polyneuropathy (AIDP; Guillain–Barré syndrome) may also look like a NMJ disease but the latter usually presents with bulbar symptoms earlier on and lacks the classic ascending paralysis pattern. Bulbar involvement in NMJ disorders helps distinguish it from myopathies.

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Muscle

Myopathy is often suggested by the presentation of fairly symmetric proximal weakness in the absence of sensory complaints. Depending on the type of myopathy, symptoms may develop acutely, or more gradually, and may or may not be associated with muscle pain and tenderness. Proximal muscle weakness often comes to medical attention as the patient begins to observe difficulty climbing stairs, getting up from a chair, or combing hair. Examination may show evidence of muscle atrophy.

Generating a differential diagnosis

As discussed earlier, traditional approaches in neurology promote the concept of identifying the salient symptoms and signs and then applying parsimony in localizing neurologic deficits. Once one generates an idea of where the deficit arises, and then places it in the context of the history, one can then generate a succinct "synthesis statement" which captures the essence of the case. This in turn leads to the consideration of the broad list of categories that apply to that specific region of the neuro-axis (e.g. toxic, metabolic, ischemic) that explain how the deficit or dysfunction occurred. We have found the following list of categories of pathologic processes, with examples of specific etiologies, to be useful in thinking about differential diagnosis:

- Structural (congenital or acquired).
- Toxic (medication/drugs, toxic substances, withdrawal states).
- Infective/post-infective (meningitis, encephalitis, sinus, osteomyelitis, abscess); viral, bacterial, parasitic/protozoal, mycobacterial, fungal, spirochete, prion, post-infective.
- Pressure effects (increased intracranial pressure, herniation, hypertension, entrapment, decreased pressure).
- Psychiatric.
- Inflammatory (post-radiation therapy, granulomatous, collagen vascular, auto-immune).
- Neoplastic/paraneoplastic.
- Degenerative (acquired or heredofamilial such as dysgenetic syndromes, neurophakomatoses).
- Vascular (ischemia, hemorrhage), including aberrations in vessels, vasculitis, vascular spasm, hematologic, embolic, thrombosis.
- Metabolic (electrolyte/liver function test abnormality, endocrine, enzyme defect/ deposition disease [lysosomal and other] mitochondrial, nutrient deficiency).
- Movement disorder (such as dystonia, chorea, dyskinesia).
- Sleep disorder.
- Congenital.
- Heredofamilial.
- Traumatic.
- Ictal.
- Demyelinating.
- Other, idiopathic.

The choice of the most likely etiologies is often dictated by knowledge about other features of the symptoms and signs such as timing issues (frequency, duration, nature of onset, and termination) or circumstances of their occurrence. For example, transient neurologic events involving altered awareness or altered behaviors conjure up very specific types of diagnostic possibilities such as seizures, conditions that cause transient increased intracranial pressure, transient ischemic attacks (TIAs), movement disorders, syncope, or psychiatric symptoms. Etiologies for symptoms that develop slowly and become progressively worse suggest expanding lesions such as a neoplasm whereas acute onset symptoms may suggest an acute ischemic stroke or intracerebral hemorrhage.

Fundamental features about the patient, such as age and gender, often play crucial roles in narrowing down diagnostic possibilities. Some diagnoses may be sex-linked genetic disorders. Some diseases only afflict patients in childhood. Other risk factors are integrated into the clinician's diagnostic process such as race, prior or current illnesses, occupation and exposures, among many other factors. On the other hand, the clinician should be cautious to avoid a narrow view about the likely diagnosis simply based upon a compelling past medical history of a given condition.

Probability dictates that more common disorders, even with more unusual presentations, are more likely to explain symptoms compared with a common presentation of a rare disorder [10]. A narrowed list of possibilities is then subjected to further clarification through the use of additional testing.

Similar to the parsimonious approach taken in trying to find the least number of explanatory localization sites, a unifying etiology is promoted wherever possible, as the most likely explanation of even diverse

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