Manifestations of multiple sclerosis in adults

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INTRODUCTION

Diseases that affect central nervous system myelin can be categorized as demyelinating (acquired, inflammatory) and dysmyelinating (abnormal formation of myelin, usually genetic basis) (table 1). The most common immune-mediated inflammatory demyelinating disease of the central nervous system is multiple sclerosis (MS).

The clinical manifestations of MS will be reviewed here. Other aspects of MS are discussed separately:

Pathogenesis and epidemiology of multiple sclerosis

Clinical presentation, course, and prognosis of multiple sclerosis in adults

Management of clinically and radiologically isolated syndromes suggestive of multiple sclerosis

Evaluation and diagnosis of multiple sclerosis in adults

Symptom management of multiple sclerosis in adults

Treatment of acute exacerbations of multiple sclerosis in adults

Initial disease-modifying therapy for relapsing-remitting multiple sclerosis in adults

Treatment of secondary progressive multiple sclerosis in adults

PRESENTATION

Most patients with MS have relapsing-remitting disease, which typically presents in a young adult with a clinically isolated syndrome suggestive of MS such as optic neuritis, long tract symptoms/signs (eg, numbness, paresthesia, or weakness), a brainstem syndrome (eg, internuclear ophthalmoplegia), or a spinal cord syndrome (eg, transverse myelitis). Approximately 5 to 10 percent of adult patients have the primary progressive form of MS, which presents with gradual accumulation of disability from the onset, without superimposed acute relapses. The most common clinical presentation of primary progressive MS is a spinal cord syndrome with spastic paraparesis and no clear sensory level [1]. (See "Clinical presentation, course, and prognosis of multiple sclerosis in adults", section on 'Disease onset and pattern' and "Management of clinically and radiologically isolated syndromes suggestive of multiple sclerosis".)

A relapse (also called an attack or exacerbation, or a clinically isolated syndrome when it is the first episode) is defined as the acute or subacute onset of a monophasic clinical episode with patient-reported symptoms and objective findings typical of MS, reflecting a focal or multifocal inflammatory demyelinating event in the central nervous system, with a duration of at least 24 hours, in the absence of fever or infection [2].

CLINICAL SYMPTOMS AND SIGNS

There are no clinical manifestations that are unique to MS, but some are highly characteristic of the disease (table 2). Common symptoms and signs of MS (table 3) include sensory symptoms in the limbs or one side of the face, visual loss, acute or subacute motor weakness, diplopia, gait disturbance and balance problems, Lhermitte sign (electric shock-like sensations that run down the back and/or limbs upon flexion of the neck), vertigo, bladder problems, limb ataxia, acute transverse myelitis, and pain [3].

Bowel and bladder dysfunction — Approximately 50 percent of patients with MS report bowel dysfunction and up to 75 percent report bladder dysfunction [4]. The extent of sphincter and sexual dysfunction often parallels the degree of motor impairment in the lower extremities. The most frequent urinary complaint is urgency,

which is usually the result of uninhibited detrusor contraction due to a suprasegmental lesion.

Urinary incontinence becomes more common as the disease progresses. (See "Chronic complications of spinal cord injury and disease", section on 'Urinary complications'.)

Neurogenic bladder dysfunction in MS can be categorized according to the underlying pathophysiologic mechanisms, which generally lead to failure of the bladder to empty or store urine [5,6]:

- Detrusor overactivity (ie, overactive bladder), leading to failure of the bladder to store urine. The resulting symptoms include urgency, frequency, and urge incontinence. Detrusor overactivity is the most common urologic abnormality affecting patients with MS, and is typically caused by cortical demyelinating lesions that impair the detrusor reflex at the level of the frontal cortex.

- Detrusor sphincter dyssynergia, the term used to describe detrusor contraction without urethral sphincter relaxation, leading to functional bladder outlet obstruction and failure to empty, typically caused by lesions involving the pontine micturition center or spinal cord lesions above the sacral parasympathetic centers. Associated symptoms include hesitancy, interrupted stream, and incomplete voiding.

- Inefficient bladder contractility, leading to failure of the bladder to empty, and attributed to lesions spinal cord lesions that disrupt coordination with the pontine micturition center. Related symptoms include incomplete emptying, residual urine, and frequency.

- Abnormal sensation and bladder hypoactivity due to involvement of sacral segments of the spinal cord, leading to failure to empty (ie, an atonic dilated bladder that empties by overflow); this condition results from loss of perception of bladder fullness, and it is usually associated with urethral, anal, and genital hypesthesia, and sensory deficits in the sacral dermatomes. Symptoms include urinary retention, interrupted micturition, and incomplete bladder emptying.

While these can exist in isolation, many patients with MS have several concurrent types of bladder dysfunction [5].

Neurogenic bowel dysfunction in patients with MS can be divided into disorders of storage and elimination [7]. These problems may be a result of both upper and lower motor neuron impairment. Constipation, poor evacuation, and incontinence are the

most common bowel disorders associated with MS, in that order. One study of 221 patients with MS found that 54 percent had constipation while 29 percent experienced fecal incontinence [8].

Cognitive impairment — Frank dementia is an uncommon feature of MS [9], occurring in fewer than 5 percent of patients. It is usually only encountered in severely affected individuals. However, when evaluated with neuropsychological tests, up to 70 percent of patients have some cognitive impairment [10]. The prevalence of cortical syndromes such as aphasia, apraxia, and agnosia is low.

Cognitive impairment may be common even at the onset of MS [11,12]. The most frequent abnormalities are in attention, executive functioning, abstract conceptualization, short term memory, word recall, and speed of information processing [12,13]. Different disease courses may have different cognitive profiles. As an example, there is evidence that patients with relapsing-remitting MS generally have better cognitive performance than patients with progressive types of MS [14,15]. Of note, subtle alterations in cognitive functioning may remain unidentified during routine office practice, notwithstanding the application of rapid assessment tools such as the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MOCA) tools. (See "Evaluation of cognitive impairment and dementia", section on 'Cognitive testing'.)

The degree of cognitive decline in patients with MS correlates with the severity of cerebral pathology and lesion burden on MRI [12,16-19], including the persistence of T1 black holes (signifying loss of tissue architecture), and atrophy of the corpus callosum and thalamus [16-24]. Cortical atrophy as measured by MRI (image 1) correlates with cognitive changes, suggesting that gray as well as white matter atrophy may contribute to the cognitive decline in patients with MS [20-24].

Depression frequently has a negative impact on cognition, particularly on memory, attention, and concentration (see 'Depression' below). Depression, lack of social support, and the presence of cognitive impairment have been shown to correlate with one another, independent of level of physical disability [25]. Depression is also correlated with use of less effective coping styles [26]. These relationships are likely quite complex and interactive.

The ability of severe clinical depression to reduce performance on neuropsychological measures is well established in healthy controls and in patients with known risk factors for cognitive dysfunction, such as those with traumatic brain injury. In patients with MS,

a number of cognitive domains related to executive functioning may be especially vulnerable to depression. These domains include working memory, planning ability, information processing speed, and nonspeeded central executive skill [27-30]. Thus, depression likely contributes to cognitive dysfunction in patients with MS, which in turn leads to impaired problem solving and poor coping in real world situations, where people have to make flexible and instantaneous coping choices.

Acute cerebral lesions occasionally manifest as a confusional state associated with progressive focal paralysis. These findings can be mistakenly attributed to a tumor [31].

The management of cognitive impairment in MS is discussed separately. (See "Symptom management of multiple sclerosis in adults", section on 'Cognitive impairment'.)

Depression — Cross-sectional studies have shown some degree of affective disturbance in up to two-thirds of patients with MS [32].

Depression may be more common in patients with MS than in others with chronic medical conditions [26,33]. In addition, the risk of suicide in patients with MS may be increased in comparison with the general population, as shown in most [34-37] but not all [38] studies. The median life expectancy in patients with MS is reduced by about 5 to 10 years compared with that of the general population [39,40]; suicide probably has only a small effect on this diminution.

Some of the numerous medical and psychiatric comorbidities that contribute to depression in MS are pain, anxiety, fatigue, substance abuse, and cognitive impairment; conversely, depression appears to have a major deleterious impact on cognitive function in patients with MS. (See 'Cognitive impairment' above.)

Early trials suggested that treatment with an interferon beta may contribute to the development or unmasking of depression, but subsequent studies have not found such an association [41-44].

The management of depression in patients with MS is reviewed elsewhere. (See "Symptom management of multiple sclerosis in adults", section on 'Depression'.)

Epilepsy — Epilepsy is more common in patients with MS than in the general population, occurring in 2 to 3 percent of patients [45]. Approximately two-thirds of seizures in patients with MS are primary or secondary generalized seizures, while the remaining one-third are partial. Simple partial seizures are about twice as common as

complex partial seizures in patients with MS. This differs from the general population, where complex partial seizures are more frequent than simple partial [45].

Seizures associated with MS are generally benign and transient and respond well to antiseizure medication therapy or require no therapy. This issue is discussed in greater detail separately. (See "Symptom management of multiple sclerosis in adults", section on 'Seizures'.)

Eye movement abnormalities — A host of efferent visual disturbances can occur as manifestations of MS, including the following [46,47]:

- Abnormalities of voluntary gaze (very common)
  - Internuclear ophthalmoplegia (see 'Internuclear ophthalmoparesis' below)
  - Ocular dysmetria and gaze impersistence
  - Horizontal gaze palsy
  - One-and-a-half syndrome
  - Dorsal midbrain syndrome
  - Skew deviation
- Nystagmus (very common)
  - Horizontal
  - Vertical
  - Pendular (see 'Pendular nystagmus' below)
  - Periodic alternating
- Abnormalities of slow phase eye movements (common)
  - Disordered smooth pursuit
- Paroxysmal disorders of eye movements (less common)
  - Ocular flutter
  - Square wave jerks
  - Opsoclonus
- Isolated ocular motor nerve palsies (uncommon)

These eye movement abnormalities can result in variable degrees of diplopia or oscillopsia (ie, the illusion of environmental movement) [47]. (See "Overview of

diplopia" and "Overview of nystagmus" and "Jerk nystagmus" and "Pendular nystagmus".)

Internuclear ophthalmoparesis — Internuclear ophthalmoparesis (INO) refers to abnormal horizontal ocular movements with lost or delayed adduction and horizontal nystagmus of the abducting eye. INO is caused by a lesion of the medial longitudinal fasciculus in the brainstem on the side of diminished adduction. Convergence is typically preserved. When present bilaterally, it is usually coupled with vertical nystagmus on upward gaze. A bilateral INO is most suggestive of MS but can also be observed with other intraaxial brainstem lesions, including brainstem glioma, vascular lesions, Arnold-Chiari malformations, and Wernicke encephalopathy. (See "Internuclear ophthalmoparesis".)

Pendular nystagmus — Approximately 2 to 4 percent of patients with MS develop acquired pendular nystagmus [48,49]; most patients with this form of nystagmus have MS [50]. It is seldom a presenting sign of MS, more typically developing later in the course of disease and persisting indefinitely, resolving in only 5 percent. (See "Pendular nystagmus", section on 'Acquired pendular nystagmus'.)

Acquired pendular nystagmus is characterized by rapid, small-amplitude pendular oscillations of the eyes in the primary position resembling quivering jelly. Patients frequently complain of oscillopsia, which impairs visual performance. Marked impairment of visual acuity may also be present, due in part to blurring from constant eye motion and perhaps also to concurrent optic neuropathy [49].

Fatigue — Fatigue is a characteristic finding in MS, usually described as physical exhaustion that is unrelated to the amount of activity performed. The impact of fatigue is suggested by the findings of a survey of 223 patients with MS; fatigue was the most common currently experienced symptom (86 percent), and it was rated as the worst symptom causing difficulty or distress by 65 percent, higher than any other symptom [3]. Fatigue interferes with daily activities.

Primary MS-related fatigue typically occurs daily and worsens as the day goes on. Many patients complain of feeling exhausted on waking, even if they have slept soundly. Fatigue can also occur during the day but may be partially or completely relieved by rest. It is often aggravated by heat and humidity. This is considered to be due to slowing of neuronal conduction with increased body temperature (see 'Heat sensitivity' below). In addition, there appears to be a correlation between fatigue and disrupted sleep in MS patients [51,52].

Fatigue is often seen in association with an acute MS attack and may precede the focal neurologic features of the attack and persist long after the attack has subsided [52]. In addition, fatigue has been correlated with measures of cerebral axonal injury, implying a central nervous system component to the development of fatigue [53]. However, there is a poor correlation between fatigue and the overall severity of MS or with the presence of any particular symptom or sign of MS.

A number of secondary problems associated with MS may also cause or worsen fatigue. Many of these are treatable and include:

- Sleep disturbances secondary to muscle spasms or bladder problems
- Depression
- Mobility limitations
- Infections
- Anemia
- Thyroid disorders and chronic thyroid infections
- Sleep apnea; central or obstructive
- Restless legs syndrome [52]
- Medications, including antihistamines, anti-inflammatory drugs, antihypertensive medications, heart medications, muscle relaxants, sedative-hypnotics (including antihistamines such as diphenhydramine) [54], and diabetes therapy

The treatment of fatigue associated with MS is discussed in elsewhere. (See "Symptom management of multiple sclerosis in adults", section on 'Fatigue'.)

Heat sensitivity — Heat sensitivity (Uhthoff phenomenon) is a well-known occurrence in MS; small increases in the body temperature can temporarily worsen current or preexisting signs and symptoms [55,56]. Transient increases in the frequency or severity of clinical signs and symptoms as a result of elevated body temperature are experienced by 60 to 80 percent of individuals with MS [57]. The temporary worsening of neurologic signs and symptoms of MS in response to heat exposure can diminish physical and cognitive function of affected patients with MS, and impede activities of daily living and other functional capabilities [57,58].

This phenomenon is presumably the result of conduction block developing in central pathways as the body temperature increases [59]. Normally, the nerve conduction safety factor decreases with increasing temperature until a point is reached at which conduction block occurs; this point of conduction block is reached at a much lower temperature in demyelinated nerves [56].

Motor symptoms — In patients with MS, paraparesis or paraplegia are more common than isolated upper extremity weakness due to the frequent occurrence of lesions in the descending motor tracts of the spinal cord. Physical findings include spasticity, usually more marked in the legs than in the arms (see 'Spasticity' below). The deep tendon reflexes are exaggerated, sustained clonus may be elicited, and extensor plantar responses are observed. All of these manifestations are commonly asymmetrical.

Occasionally, deep tendon reflexes are decreased due to lesions interrupting the reflex arc at a segmental level, and an inverted triceps reflex may be observed. In it, the triceps contraction is lost and the efferent component is represented by a contraction of the biceps muscle. The Achilles reflex can be absent due to lesions of the sacral segments of the spinal cord, with or without concomitant sphincter and sexual problems. Occasionally, reduced reflexes reflect hypotonia resulting from cerebellar pathway lesions.

Amyotrophy can occur and is usually of the disuse type, most frequently affecting the small muscles of the hand. Less commonly, lesions of the motor root exit zones cause muscle denervation due to axon loss. Secondary entrapment neuropathies are also a cause of muscle atrophy in MS.

Brainstem-related symptoms like dysphagia, dysarthria, and respiratory dysfunction (particularly poor cough and inability to clear secretions) can occur in advanced MS disease.

Incoordination — Gait imbalance, difficulty in performing coordinated actions with the arms and hands, and slurred speech often occur as a result of impairment of cerebellar pathways. Cerebellar signs are usually mixed with pyramidal (corticospinal) tract signs.

Physical examination typically reveals dysmetria, decomposition of complex movements, and hypotonia, most often observed in the upper extremities. An intention tremor may be noted in the limbs and in the head; tremor affects 45 percent of patients with MS, with severe tremor in 6 percent [60]. Walking is impaired by truncal ataxia. Ocular findings of nystagmus, ocular dysmetria, and failure of fixation suppression (square wave jerks) suggest cerebellar or cerebello-vestibular connection dysfunction. Speech can be scanning or explosive in character. In severe cases there is complete astasia (inability to stand), inability to use the arms due to a violent intention tremor, and virtually incomprehensible speech.

Spasticity — Spasticity affects a majority of patients with MS. In a registry of over 20,000 patients with MS who reported symptoms by completing a questionnaire, the degree and frequency of spasticity were as follows [61]:

- No spasticity, 16 percent
- Minimal (does not interfere with activities), 31 percent
- Mild (occasionally affects activities), 19 percent
- Moderate (frequently affects activities), 17 percent
- Severe (need to modify daily activities), 13 percent
- Total (prevents daily activities), 4 percent

The increased muscle tone underlying spasticity is due to an upper motor neuron lesion caused by demyelination of the corticospinal system, which leads to release of inhibition on the local spinal neurons and sensory afferent pathways. Other proposed mechanisms of spasticity include prolonged motor neuron discharge, connective tissue changes, and abnormal muscle coactivation [62,63].

Some experts recognize two types of spasticity:

- Tonic spasticity, characterized by resistance to movement that is rate dependent
- Phasic spasticity, which manifests as involuntary jerks and spasms that principally affect the limbs and are more pronounced at night when attempting to sleep

The legs are most commonly affected by both forms of spasticity, but alternate patterns are recognized. Other affected regions include the cervical neck muscles, the pelvic floor, fingers and toes, and the axial paravertebral muscles.

When spasticity is severe, extensor spasms of the legs and sometimes the trunk may be provoked by active or passive attempts to rise from a bed or wheelchair.

In clinical practice, spasticity is graded by using the Modified Ashworth scale, as shown in the table (table 4).

Pain — Pain is a common symptom in patients with MS [64,65]. A systematic review and meta-analysis of pain in adults with MS found 28 studies that met inclusion criteria with over 7000 subjects [65]. The pooled overall prevalence of pain was 63 percent. Types of pain and their prevalence in this population were as follows:

- Headache in 43 percent
- Neuropathic extremity pain in 26 percent

- Back pain in 20 percent
- Lhermitte sign in 16 percent
- Painful spasms in 15 percent
- Trigeminal neuralgia in 4 percent

Pain associated with MS can arise from neurogenic and non-neurogenic sources [66]. Neurogenic pain includes paroxysmal pain, persistent pain (eg, burning or ice-cold dysesthesias of the feet, hands, limbs, and trunk), and episodic neuropathic pain. Musculoskeletal and soft tissue pain may be caused by paralysis, immobility, or spasticity.

A phenomenon referred to as the "MS hug" or as the "Anaconda sign" is variably attributed to neuropathic pain or to spasticity of the thoracic and abdominal muscles; it consists of gripping, squeezing, and constricting sensations, and is often uncomfortable or painful. (See "Symptom management of multiple sclerosis in adults", section on 'Pain'.)

Paroxysmal symptoms — Paroxysmal attacks of motor or sensory phenomena can occur with demyelinating lesions. These symptoms are characterized by brief, almost stereotypic, events occurring frequently and often triggered by movement or sensory stimuli [67]. They are likely caused by ephaptic transmission of nerve impulses at sites of previous disease activity. Although troublesome to the patient, these symptoms do not indicate a true exacerbation of MS or cause a loss of myelin in the central nervous system.

Within the brainstem, lesions may cause paroxysmal diplopia, facial paresthesia, trigeminal neuralgia, ataxia, and dysarthria. Motor system involvement results in painful tonic spasms of muscles of one or two (homolateral) limbs, trunk, and occasionally the face, but these only rarely occur in all four limbs or the trunk. These paroxysmal attacks typically respond to low doses of carbamazepine and frequently remit after several weeks to months, usually without recurrence. These symptoms and their management are discussed in greater detail separately. (See "Symptom management of multiple sclerosis in adults", section on 'Paroxysmal motor and sensory symptoms'.)

Lhermitte sign — The Lhermitte sign is a transient sensory symptom described as an electric shock radiating down the spine or into the limbs most often after flexion of the neck [68]. It may be infrequent or occur with the least movement of the head or neck. Although most frequently encountered in MS, this symptom also can be seen with

other lesions of the cervical cord, including tumors, cervical disc herniation, postradiation myelopathy, and following trauma.

Sensory symptoms — Sensory symptoms are the most common initial feature of MS (table 3) and are present in almost every patient at some time during the course of disease. The sensory features can reflect spinothalamic, posterior column, or dorsal root entry zone lesions. Symptoms are commonly described as numbness, tingling, pins-and-needles, tightness, coldness, or swelling of the limbs or trunk. Radicular pains also can be present, particularly in the low thoracic and abdominal regions. An intense itching sensation, especially in the cervical dermatomes and usually unilateral, is suggestive of MS.

The most common sensory abnormalities on clinical examination include:

- Varying degrees of impairment of vibration and joint position sense
- Decreased pain and light touch perception in a distal distribution in the four extremities
- Patchy areas of reduced pain and light touch perception in the limbs and trunk

Upon testing sensation with a sharp object such as a pin, patients frequently report that the sharp feeling is increased, or that it feels like a mild electric shock, or that the stimulus spreads in a ripple fashion from the point at which it is applied. A bilateral sensory level is more common than a hemisensory syndrome. The latter is termed a Brown-Séquard syndrome when it is coupled with contralateral weakness. (See "Anatomy and localization of spinal cord disorders", section on 'Brown-Sequard (hemicord) syndrome'.)

Impairment of facial sensation, subjective or objective, is a relatively common finding in MS. Trigeminal neuralgia (see "Trigeminal neuralgia") in a young adult may be an early sign of MS. Facial myokymia, a fine undulating wave-like facial twitching, and hemifacial spasm also can be due to MS, but other causes of a focal brainstem lesion must be excluded. Unilateral facial paresis can occur, and taste sensation is sometimes affected [69].

Sexual dysfunction — Sexual dysfunction is common in patients with MS [70]. About 50 percent of patients become completely sexually inactive secondary to their disease, and an additional 20 percent become sexually less active [8]. In men with MS, the most common complaints are reduced libido, erectile impotence, the disappearance of early morning erection, premature ejaculation, orgasmic dysfunction, and reduced penile sensation. In women with MS, the most common complaints are reduced libido,

difficulties in achieving orgasm, decreased vaginal lubrication, decreased vaginal sensation, and dyspareunia [71].

Sexual dysfunction can be the result of multiple problems, including the direct effects of lesions of the motor and sensory pathways within the spinal cord and psychological factors involved with self-image, self-esteem, and fear of rejection from the sexual partner [71]. Mechanical problems created by spasticity, paraparesis, and incontinence further aggravate the problem.

Sphincter and sexual dysfunction associated with MS are discussed in greater detail separately. (See "Symptom management of multiple sclerosis in adults", section on 'Sexual dysfunction' and "Symptom management of multiple sclerosis in adults", section on 'Bladder dysfunction'.)

Sleep disorders — A 2015 systematic review identified 18 studies evaluating the prevalence of sleep disorders in subjects with MS [72]. Most of the studies were based in MS clinics; none were population-based. Studies of sleep quality or insomnia were not reviewed because of variable definitions of these conditions. The main sleep disorders and their prevalence ranges were the following:

- Restless legs syndrome, 14 to 58 percent (12 studies)
- Obstructive sleep apnea, 7 to 58 percent (5 studies)
- Periodic limb movements of sleep, 36 percent (1 study)
- Rapid eye movement sleep behavior disorder, 2 to 3 percent (2 studies)
- Narcolepsy, 0 to 2 percent (2 studies)

Given the lack of population-based studies, the true incidence and prevalence of these disorders in the MS population is unknown [72].

A substantial proportion of patients with MS suffer from insomnia with difficulty initiating and maintaining sleep. Limited data suggest that the prevalence of insomnia in MS is as high as 40 percent, or several times higher than the prevalence in the general population [73-76]. Factors contributing to insomnia include the following:

- Pain syndromes (eg, muscle spasms, Lhermitte sign, and trigeminal neuralgia)
- Restless legs syndrome
- Nocturia
- Medication side effects, particularly stimulant medications used to treat fatigue
- Psychiatric syndromes (eg, anxiety and depression)

The prevalence of restless legs syndrome in patients with MS is estimated to be fourfold higher compared with the general population (19 versus 4.2 percent, respectively) [77]. Therefore, patients with MS who complain of insomnia and excessive daytime somnolence should be evaluated for restless legs syndrome [78]; the diagnosis is made by history. Patients with MS and restless legs syndrome may have more cervical cord lesions than do those patients with MS who do not have restless legs syndrome, as revealed by conventional and non-conventional MRI techniques [79]. (See "Clinical features and diagnosis of restless legs syndrome and periodic limb movement disorder in adults".)

Nocturia and pain frequently interrupt sleep in patients with MS. Nocturia affects as many as 70 to 80 percent of patients with MS [80]. Pain can disrupt sleep, causing daytime somnolence and worsening fatigue as well as reducing pain threshold.

Vertigo — Vertigo is a reported symptom in 30 to 50 percent of patients with MS. One retrospective study found that the most common cause of vertigo in patients with MS was benign positional paroxysmal vertigo [81]. However, vertigo is often directly related to the development of demyelinating plaques in the vestibular pathways such as the medullary tegmentum and the root entry zone of the eighth cranial nerve in the pontomedullary junction, or to other demyelinating brain stem lesions. In such cases, vertigo may be associated with symptoms reflecting dysfunction of adjacent cranial nerves such as hyper- or hypoacusis, facial numbness, and diplopia.

Vertigo from a demyelinating lesion tends to last for a longer duration (hours to days) and typically does not have positional triggers when compared with benign positional paroxysmal vertigo (BPPV), which is a common misdiagnosis in this setting. (See "Benign paroxysmal positional vertigo".)

Visual symptoms — Optic neuritis is the most common type of involvement of the visual pathways with MS (see "Optic neuritis: Pathophysiology, clinical features, and diagnosis"). Optic neuritis usually presents as acute or subacute unilateral eye pain that is accentuated by ocular movements [82]. This is followed by a variable degree of visual loss (scotoma) affecting mainly central vision. Bilateral simultaneous optic neuritis is rare in MS; its occurrence in isolation may suggest another diagnosis such as Leber hereditary optic atrophy, toxic optic neuropathy, or neuromyelitis optica (NMO) spectrum disease. When bilateral optic neuritis occurs in patients with MS, the impairment begins asymmetrically and is usually more severe in one eye.

Physical examination of patients with optic neuritis reveals a relative afferent pupillary defect (Marcus-Gunn pupil), which is evaluated with the swinging flashlight test (figure 1 and picture 1). When the acute optic neuritis lesion involves the head of the optic nerve, disc edema may be observed on fundus examination, a finding more common in children than in adults. Most often the lesion of the optic nerve is retrobulbar, and in the acute stage fundus examination is normal. Later the optic disc becomes pale as a result of axonal loss and resultant gliosis. This pallor predominates in the temporal segment of the disc (temporal pallor).

Ninety percent of patients regain normal vision over a period of two to six months after an acute episode of optic neuritis. Desaturation of bright colors, particularly red, is often reported by recovered patients; some also report a mild nonspecific dimming. (See "Optic neuritis: Prognosis and treatment", section on 'Prognosis'.)

Patients with MS might also report an interesting visual phenomenon called the Pulfrich phenomenon, which is an illusory perception that an object moving linearly along a two-dimensional plane appears to instead follow an elliptical three-dimensional trajectory [67,83]. This phenomenon is a consequence of inter-eye asymmetry in the timing of visual object identification in the visual cortex, with optic neuritis as a common etiology.

Bitemporal hemianopia is rare in MS and, if present, should raise the suspicion of a mass lesion compressing the visual pathways. Homonymous field defects are uncommon but can be seen in MS due to involvement of the optic radiations.

DIAGNOSIS

Multiple sclerosis is a clinical diagnosis. The core requirement of the diagnosis is the demonstration of central nervous system lesion dissemination in time and space. The diagnosis of MS is discussed in detail elsewhere. (See "Evaluation and diagnosis of multiple sclerosis in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a

general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Multiple sclerosis in adults (The Basics)")

SUMMARY

- **Presentation** – Most patients with multiple sclerosis (MS) have relapsing-remitting disease, which often begins in a young adult with a clinically isolated syndrome suggestive of MS such as optic neuritis, long tract symptoms/signs, a brainstem syndrome (eg, internuclear ophthalmoplegia), or a spinal cord syndrome (eg, transverse myelitis). (See "Clinical presentation, course, and prognosis of multiple sclerosis in adults", section on 'Clinically isolated syndrome'.)

  The typical patient with relapsing-remitting MS presents as a young adult with two or more clinically distinct episodes of central nervous system dysfunction with at least partial resolution. A minority of adult patients have the primary progressive form of MS, which presents with gradual accumulation of disability from the onset. (See 'Presentation' above.)

- **Symptoms and signs** – There are no clinical findings that are unique to MS, but some are highly characteristic of the disease (table 2). Common manifestations of MS (table 3) include the following (see 'Clinical symptoms and signs' above):

  - Bowel and bladder dysfunction (see 'Bowel and bladder dysfunction' above)
  - Cognitive impairment (see 'Cognitive impairment' above)
  - Fatigue (see 'Fatigue' above)
  - Gait disturbance and balance problems (see 'Incoordination' above)
  - Heat sensitivity (see 'Heat sensitivity' above)

- Motor symptoms (see 'Motor symptoms' above)
- Pain (see 'Pain' above)
- Paroxysmal symptoms (see 'Paroxysmal symptoms' above)
- Sensory symptoms (see 'Sensory symptoms' above)
- Sexual dysfunction (see 'Sexual dysfunction' above)
- Vertigo (see 'Vertigo' above)
- Visual disturbances (see 'Eye movement abnormalities' above and 'Visual symptoms' above)

REFERENCES

1. Rice CM, Cottrell D, Wilkins A, Scolding NJ. Primary progressive multiple sclerosis: progress and challenges. J Neurol Neurosurg Psychiatry 2013; 84:1100.
2. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018; 17:162.
3. Richards RG, Sampson FC, Beard SM, Tappenden P. A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models. Health Technol Assess 2002; 6:1.
4. DasGupta R, Fowler CJ. Bladder, bowel and sexual dysfunction in multiple sclerosis: management strategies. Drugs 2003; 63:153.
5. Wintner A, Kim MM, Bechis SK, Kreydin EI. Voiding Dysfunction in Multiple Sclerosis. Semin Neurol 2016; 36:34.
6. Yang CC. Bladder management in multiple sclerosis. Phys Med Rehabil Clin N Am 2013; 24:673.
7. Frohman TC, Castro W, Shah A, et al. Symptomatic therapy in multiple sclerosis. Ther Adv Neurol Disord 2011; 4:83.
8. Hennessey A, Robertson NP, Swingler R, Compston DA. Urinary, faecal and sexual dysfunction in patients with multiple sclerosis. J Neurol 1999; 246:1027.
9. Staff NP, Lucchinetti CF, Keegan BM. Multiple sclerosis with predominant, severe cognitive impairment. Arch Neurol 2009; 66:1139.

10. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. Lancet Neurol 2008; 7:1139.
11. Achiron A, Barak Y. Cognitive impairment in probable multiple sclerosis. J Neurol Neurosurg Psychiatry 2003; 74:443.
12. Deloire MS, Salort E, Bonnet M, et al. Cognitive impairment as marker of diffuse brain abnormalities in early relapsing remitting multiple sclerosis. J Neurol Neurosurg Psychiatry 2005; 76:519.
13. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology 1991; 41:685.
14. Huijbregts SC, Kalkers NF, de Sonneville LM, et al. Differences in cognitive impairment of relapsing remitting, secondary, and primary progressive MS. Neurology 2004; 63:335.
15. Ruet A, Deloire M, Charré-Morin J, et al. Cognitive impairment differs between primary progressive and relapsing-remitting MS. Neurology 2013; 80:1501.
16. Franklin GM, Heaton RK, Nelson LM, et al. Correlation of neuropsychological and MRI findings in chronic/progressive multiple sclerosis. Neurology 1988; 38:1826.
17. Hohol MJ, Guttmann CR, Orav J, et al. Serial neuropsychological assessment and magnetic resonance imaging analysis in multiple sclerosis. Arch Neurol 1997; 54:1018.
18. Rao SM, Leo GJ, Haughton VM, et al. Correlation of magnetic resonance imaging with neuropsychological testing in multiple sclerosis. Neurology 1989; 39:161.
19. Calabrese M, Agosta F, Rinaldi F, et al. Cortical lesions and atrophy associated with cognitive impairment in relapsing-remitting multiple sclerosis. Arch Neurol 2009; 66:1144.
20. Amato MP, Bartolozzi ML, Zipoli V, et al. Neocortical volume decrease in relapsing-remitting MS patients with mild cognitive impairment. Neurology 2004; 63:89.
21. Sanfilipo MP, Benedict RH, Weinstock-Guttman B, Bakshi R. Gray and white matter brain atrophy and neuropsychological impairment in multiple sclerosis. Neurology 2006; 66:685.
22. Calabrese M, Rinaldi F, Mattisi I, et al. Widespread cortical thinning characterizes patients with MS with mild cognitive impairment. Neurology 2010; 74:321.
23. Filippi M, Rocca MA, Benedict RH, et al. The contribution of MRI in assessing cognitive impairment in multiple sclerosis. Neurology 2010; 75:2121.

24. Mesaros S, Rocca MA, Kacar K, et al. Diffusion tensor MRI tractography and cognitive impairment in multiple sclerosis. Neurology 2012; 78:969.
25. Gilchrist AC, Creed FH. Depression, cognitive impairment and social stress in multiple sclerosis. J Psychosom Res 1994; 38:193.
26. Mohr DC, Goodkin DE, Gatto N, Van der Wende J. Depression, coping and level of neurological impairment in multiple sclerosis. Mult Scler 1997; 3:254.
27. Arnett PA, Higginson CI, Randolph JJ. Depression in multiple sclerosis: relationship to planning ability. J Int Neuropsychol Soc 2001; 7:665.
28. Arnett PA, Higginson CI, Voss WD, et al. Depressed mood in multiple sclerosis: relationship to capacity-demanding memory and attentional functioning. Neuropsychology 1999; 13:434.
29. Thornton AE, Raz N. Memory impairment in multiple sclerosis: a quantitative review. Neuropsychology 1997; 11:357.
30. Arnett PA, Higginson CI, Voss WD, et al. Depression in multiple sclerosis: relationship to working memory capacity. Neuropsychology 1999; 13:546.
31. Zagzag D, Miller DC, Kleinman GM, et al. Demyelinating disease versus tumor in surgical neuropathology. Clues to a correct pathological diagnosis. Am J Surg Pathol 1993; 17:537.
32. Rao SM, Reingold SC, Ron MA, et al. Workshop on Neurobehavioral Disorders in Multiple Sclerosis. Diagnosis, underlying disease, natural history, and therapeutic intervention, Bergamo, Italy, June 25-27, 1992. Arch Neurol 1993; 50:658.
33. Patten SB, Beck CA, Williams JV, et al. Major depression in multiple sclerosis: a population-based perspective. Neurology 2003; 61:1524.
34. Sadovnick AD, Eisen K, Ebers GC, Paty DW. Cause of death in patients attending multiple sclerosis clinics. Neurology 1991; 41:1193.
35. Stenager EN, Stenager E. Suicide and patients with neurologic diseases. Methodologic problems. Arch Neurol 1992; 49:1296.
36. Fredrikson S, Cheng Q, Jiang GX, Wasserman D. Elevated suicide risk among patients with multiple sclerosis in Sweden. Neuroepidemiology 2003; 22:146.
37. Brønnum-Hansen H, Stenager E, Nylev Stenager E, Koch-Henriksen N. Suicide among Danes with multiple sclerosis. J Neurol Neurosurg Psychiatry 2005; 76:1457.
38. Sumelahti ML, Tienari PJ, Wikström J, et al. Survival of multiple sclerosis in Finland between 1964 and 1993. Mult Scler 2002; 8:350.

39. Brønnum-Hansen H, Koch-Henriksen N, Stenager E. Trends in survival and cause of death in Danish patients with multiple sclerosis. Brain 2004; 127:844.
40. Compston A, Coles A. Multiple sclerosis. Lancet 2008; 372:1502.
41. Patten SB, Metz LM, SPECTRIMS Study Group. Interferon beta1a and depression in secondary progressive MS: data from the SPECTRIMS Trial. Neurology 2002; 59:744.
42. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive MS. Lancet 1998; 352:1491.
43. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol 1996; 39:285.
44. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet 1998; 352:1498.
45. Koch M, Uyttenboogaart M, Polman S, De Keyser J. Seizures in multiple sclerosis. Epilepsia 2008; 49:948.
46. Barnes D, McDonald WI. The ocular manifestations of multiple sclerosis. 2. Abnormalities of eye movements. J Neurol Neurosurg Psychiatry 1992; 55:863.
47. Frohman EM, Frohman TC, Zee DS, et al. The neuro-ophthalmology of multiple sclerosis. Lancet Neurol 2005; 4:111.
48. Aschoff JC, Conrad B, Kornhuber HH. Acquired pendular nystagmus with oscillopsia in multiple sclerosis: a sign of cerebellar nuclei disease. J Neurol Neurosurg Psychiatry 1974; 37:570.
49. Barton JJ, Cox TA. Acquired pendular nystagmus in multiple sclerosis: clinical observations and the role of optic neuropathy. J Neurol Neurosurg Psychiatry 1993; 56:262.
50. Gresty MA, Ell JJ, Findley LJ. Acquired pendular nystagmus: its characteristics, localising value and pathophysiology. J Neurol Neurosurg Psychiatry 1982; 45:431.
51. Attarian HP, Brown KM, Duntley SP, et al. The relationship of sleep disturbances and fatigue in multiple sclerosis. Arch Neurol 2004; 61:525.
52. Čarnická Z, Kollár B, Šiarnik P, et al. Sleep disorders in patients with multiple sclerosis. J Clin Sleep Med 2015; 11:553.

53. Tartaglia MC, Narayanan S, Francis SJ, et al. The relationship between diffuse axonal damage and fatigue in multiple sclerosis. Arch Neurol 2004; 61:201.
54. Braley TJ, Segal BM, Chervin RD. Hypnotic use and fatigue in multiple sclerosis. Sleep Med 2015; 16:131.
55. Selhorst JB, Saul RF. Uhthoff and his symptom. J Neuroophthalmol 1995; 15:63.
56. Frohman TC, Davis SL, Beh S, et al. Uhthoff's phenomena in MS--clinical features and pathophysiology. Nat Rev Neurol 2013; 9:535.
57. Syndulko K, Jafari M, Woldanski A, et al. Effects of temperature in multiple sclerosis: A review of the literature. Neurorehabil Neural Repair 1996; 10:23.
58. Davis SL, Wilson TE, White AT, Frohman EM. Thermoregulation in multiple sclerosis. J Appl Physiol (1985) 2010; 109:1531.
59. Humm AM, Beer S, Kool J, et al. Quantification of Uhthoff's phenomenon in multiple sclerosis: a magnetic stimulation study. Clin Neurophysiol 2004; 115:2493.
60. Rinker JR 2nd, Salter AR, Walker H, et al. Prevalence and characteristics of tremor in the NARCOMS multiple sclerosis registry: a cross-sectional survey. BMJ Open 2015; 5:e006714.
61. Rizzo MA, Hadjimichael OC, Preiningerova J, Vollmer TL. Prevalence and treatment of spasticity reported by multiple sclerosis patients. Mult Scler 2004; 10:589.
62. Thompson AJ, Jarrett L, Lockley L, et al. Clinical management of spasticity. J Neurol Neurosurg Psychiatry 2005; 76:459.
63. Trompetto C, Marinelli L, Mori L, et al. Pathophysiology of spasticity: implications for neurorehabilitation. Biomed Res Int 2014; 2014:354906.
64. Drulovic J, Basic-Kes V, Grgic S, et al. The Prevalence of Pain in Adults with Multiple Sclerosis: A Multicenter Cross-Sectional Survey. Pain Med 2015; 16:1597.
65. Foley PL, Vesterinen HM, Laird BJ, et al. Prevalence and natural history of pain in adults with multiple sclerosis: systematic review and meta-analysis. Pain 2013; 154:632.
66. Kahraman T, Özdoğar AT, Ertekin Ö, Özakbaş S. Frequency, type, distribution of pain and related factors in persons with multiple sclerosis. Mult Scler Relat Disord 2019; 28:221.
67. Rae-Grant AD. Unusual symptoms and syndromes in multiple sclerosis. Continuum (Minneap Minn) 2013; 19:992.
68. Kanchandani R, Howe JG. Lhermitte's sign in multiple sclerosis: a clinical survey and review of the literature. J Neurol Neurosurg Psychiatry 1982; 45:308.

69. McGraw C, Krieger S, Wong J, Fabian M. The food critic who couldn't taste and 6 other cases of dysgeusia in multiple sclerosis. Neurology 2012; 78(Meeting Abstracts 1):P06.178. www.neurology.org/cgi/content/meeting_abstract/78/1_MeetingAbstracts/P06.178 (Accessed on March 10, 2015).

70. Lew-Starowicz M, Gianotten WL. Sexual dysfunction in patients with multiple sclerosis. Handb Clin Neurol 2015; 130:357.

71. Zivadinov R, Zorzon M, Bosco A, et al. Sexual dysfunction in multiple sclerosis: II. Correlation analysis. Mult Scler 1999; 5:428.

72. Marrie RA, Reider N, Cohen J, et al. A systematic review of the incidence and prevalence of sleep disorders and seizure disorders in multiple sclerosis. Mult Scler 2015; 21:342.

73. Tachibana N, Howard RS, Hirsch NP, et al. Sleep problems in multiple sclerosis. Eur Neurol 1994; 34:320.

74. Brass SD, Duquette P, Proulx-Therrien J, Auerbach S. Sleep disorders in patients with multiple sclerosis. Sleep Med Rev 2010; 14:121.

75. Stanton BR, Barnes F, Silber E. Sleep and fatigue in multiple sclerosis. Mult Scler 2006; 12:481.

76. Caminero A, Bartolomé M. Sleep disturbances in multiple sclerosis. J Neurol Sci 2011; 309:86.

77. Schürks M, Bussfeld P. Multiple sclerosis and restless legs syndrome: a systematic review and meta-analysis. Eur J Neurol 2013; 20:605.

78. Trojan DA, Da Costa D, Bar-Or A, et al. Sleep abnormalities in multiple sclerosis patients. Mult Scler 2008; 14:S160.

79. Manconi M, Rocca MA, Ferini-Strambi L, et al. Restless legs syndrome is a common finding in multiple sclerosis and correlates with cervical cord damage. Mult Scler 2008; 14:86.

80. Amarenco G, Kerdraon J, Denys P. [Bladder and sphincter disorders in multiple sclerosis. Clinical, urodynamic and neurophysiological study of 225 cases]. Rev Neurol (Paris) 1995; 151:722.

81. Frohman EM, Zhang H, Dewey RB, et al. Vertigo in MS: utility of positional and particle repositioning maneuvers. Neurology 2000; 55:1566.

82. Balcer LJ. Clinical practice. Optic neuritis. N Engl J Med 2006; 354:1273.

83. Sobhanian MJ, Agarwal R, Meltzer E, et al. Identification and treatment of the visual processing asymmetry in MS patients with optic neuritis: The Pulfrich

phenomenon. J Neurol Sci 2018; 387:60.

Topic 1689 Version 49.0

GRAPHICS

Diseases of myelin

Dysmyelinating
Adrenoleukodystrophy
Metachromatic leukodystrophy
Krabbe disease
Alexander disease
Canavan van Bogaert disease
Pelizaeus-Merzbacher disease
Phenylketonuria
Demyelinating
Autoimmune
Acute disseminated encephalomyelitis
Acute hemorrhagic leukoencephalopathy
Multiple sclerosis
Neuromyelitis optica
Infectious
Progressive multifocal leukoencephalopathy
Toxic/metabolic
Carbon monoxide
Vitamin B12 deficiency
Mercury intoxication (Minamata disease)
Alcohol/tobacco amblyopia
Central pontine myelinolysis
Marchiafava-Bignami syndrome
Hypoxia
Radiation
Vascular
Binswanger disease

Graphic 80553 Version 4.0

Suggestive and atypical features of multiple sclerosis

Features suggestive of multiple sclerosis
Relapses and remissions
Onset between ages 15 and 50 years
Optic neuritis
Lhermitte sign
Internuclear ophthalmoplegia
Fatigue
Heat sensitivity (Uhthoff phenomenon)
Features atypical for multiple sclerosis
Steady progression
Onset before age 10 or after age 50 years
Cortical deficits such as aphasia, apraxia, alexia, or neglect
Rigidity or sustained dystonia
Convulsions
Early dementia
Deficit developing within minutes

Graphic 63940 Version 6.0

Manifestations of multiple sclerosis

Symptoms and signs	Total (percent)
Sensory in limbs	31
Visual loss	16
Motor (subacute)	9
Diplopia	7
Gait disturbance	5
Motor (acute)	4
Balance problems	3
Sensory in face	3
Lhermitte sign (electric shock-like sensations that run down the back and/or limbs upon flexion of the neck)	2
Vertigo	2
Bladder problems	1
Limb ataxia	1
Acute transverse myelopathy	1
Pain	<1
Other	3
Polysymptomatic onset	14

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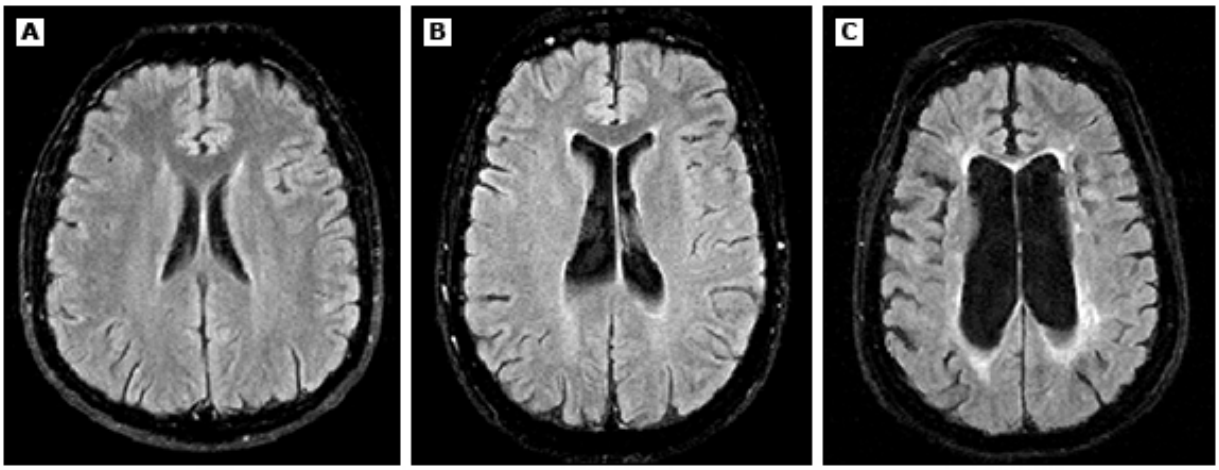
Graphic 61789 Version 5.0

Brain atrophy in multiple sclerosis on MRI



These brain MRI images were acquired over the course of seven years from a single untreated patient with multiple sclerosis, and show progression of generalized brain atrophy from the first scan (left panel) to the most recent (right panel).

MRI: magnetic resonance imaging.

Graphic 58083 Version 4.0

Modified Ashworth scale for grading spasticity[1]

Grade	Description
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

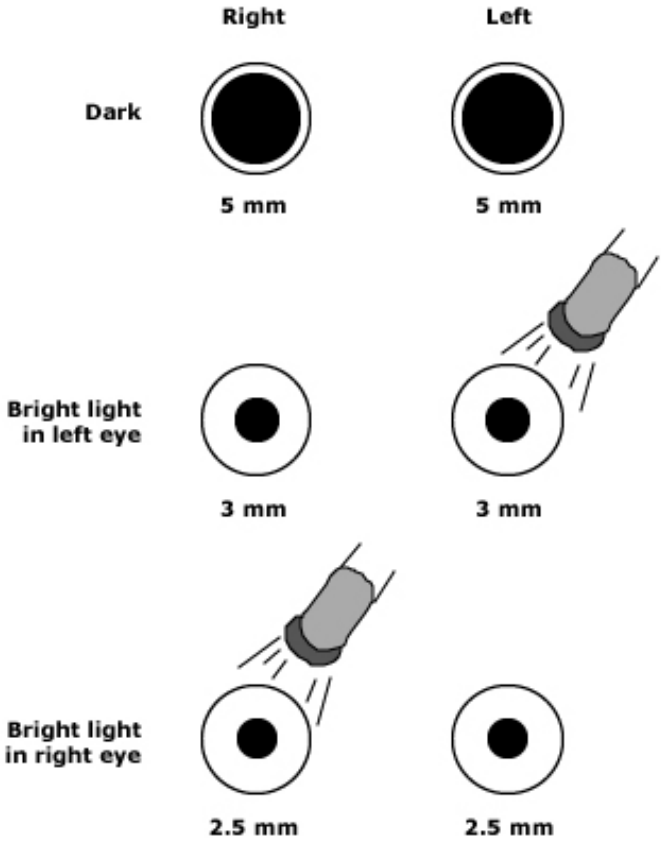
ROM: range of motion.

Reference:

1. *Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 1987; 67:206.*

Graphic 93413 Version 3.0

Left afferent pupillary defect



The left pupil is the same size as the right under all conditions of illumination because the efferent pathways are intact, but both pupils are smaller when light is directed at the right eye than when it is directed at the left eye, because light is detected better by the right eye. Alternate swinging of the light between the two eyes therefore produces dilation each time the light is directed to the left eye.

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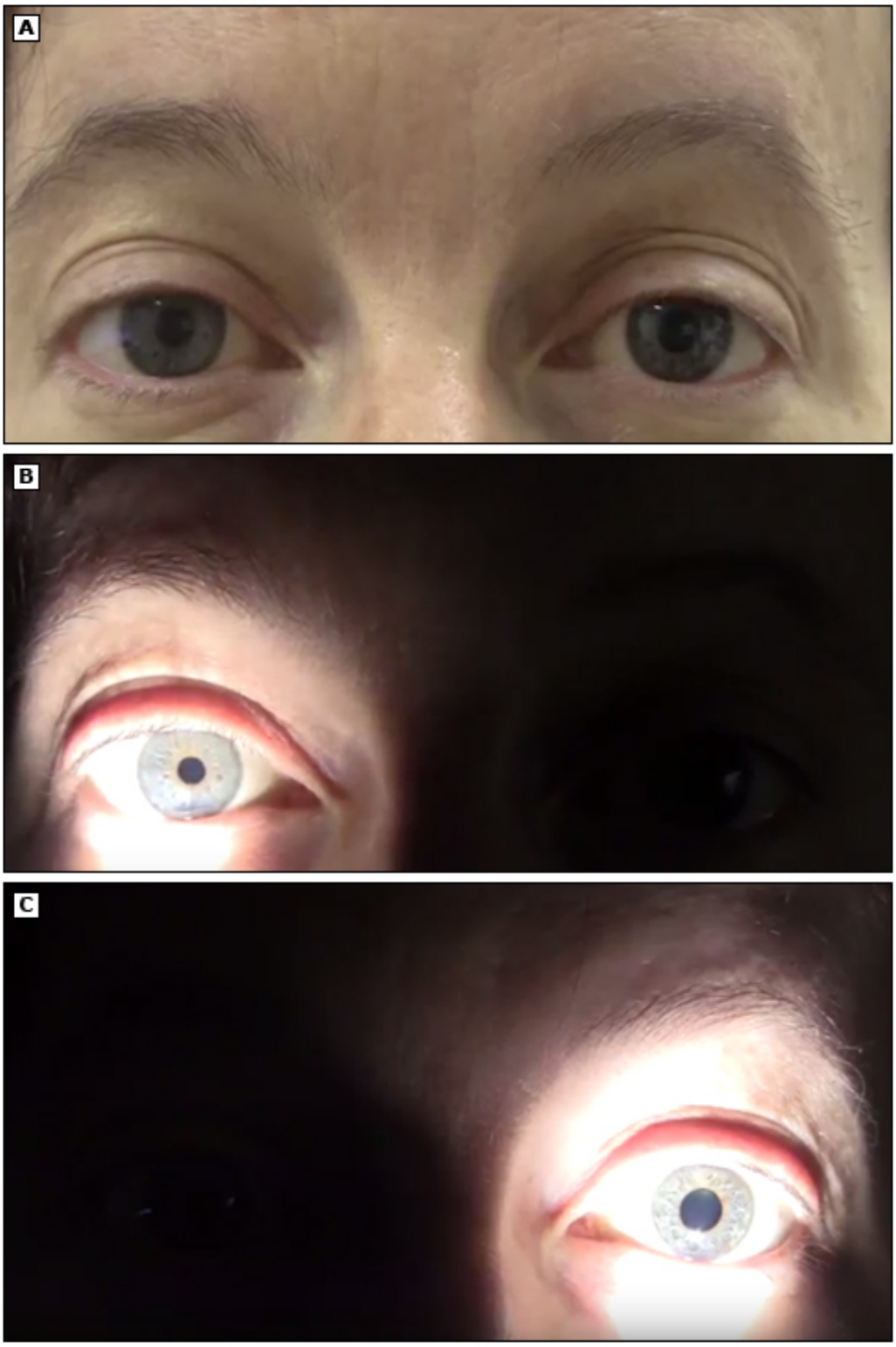
Graphic 71937 Version 4.0

Swinging flashlight test for Marcus-Gunn pupil



(A) In bright light, each eye perceives the same amount of light on average. As such, the pupils are equal in size.

(B) When the light is shone in the unaffected eye, it constricts normally.

(C) When the light is swung from the unaffected eye and shone in the affected eye, it perceives less light and both pupils paradoxically dilate.

Graphic 102285 Version 5.0

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Conflict of interest policy

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