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Weakness

Chapter: Weakness

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Definition of the symptom

Motor weakness is a decrease in muscle strength leading to an inability of a muscle or group of muscles to perform its usual function.

Differential diagnosis

The differential diagnosis of motor weakness ordered by probability is detailed in Box 44.1.

Box 44.1 Causes of motor weakness and main differential diagnoses

Cause of motor weakness

- central nervous system disorders

- peripheral nerve disorders
- neuromuscular junction disorders
- muscle disorders
- anterior horn cell disorders

Main differential diagnoses

- acute stroke or TIA
- brain tumour (primary or metastatic)
- demyelination (e.g. multiple sclerosis)
- generalized polyneuropathy (various causes)
- multiple mononeuropathy (various causes)
- plexopathy (various causes)
- myasthenia gravis
- botulism
- Lambert–Easton myasthenic syndrome
- muscular dystrophies
- other myopathies (various causes)
- motor neuron disease; amyotrophic lateral sclerosis
- poliomyelitis

Various causes of motor weakness (Box 44.1) may be encountered in the primary and secondary care setting. Acute onset weakness is more frequently encountered in secondary care, whereas weakness of an insidious onset can present to both primary and secondary care.

CNS lesions may be caused by vascular disorders (haematoma, ischaemia), tumours, cysts, infections, cavitation/syrinx (spinal cord and brainstem), inflammation, or demyelination. Lesions in the brainstem are often vascular, inflammatory/demyelinating, or malignant in origin.

The list of conditions causing weakness associated with a generalized polyneuropathy is extensive and includes Guillain–Barré Syndrome (GBS), neuropathies associated with the vasculitides and connective tissue disorders, multifocal motor neuropathy, nutritional deficiencies (B_{12}, thiamine), drug or toxin-induced weakness (vinca alkaloids, isoniazid, heavy metals), malignancy (infiltrative and paraneoplastic), renal failure, endocrine disorders (hypothyroid or hyperthyroid), sarcoidosis, diabetes, paraprotein-related weakness, and amyloidosis. The most common hereditary neuropathy is Charcot–Marie–Tooth disease (CMT, or hereditary motor and sensory neuropathy).

Conditions that can affect the peripheral nerves in an asymmetrical pattern giving rise to a multiple mononeuropathy include vasculitides, connective tissue diseases, diabetes, sarcoidosis, Lyme disease, malignant infiltrative disease, HIV, and hepatitis C infection. Disorders of the cervical, brachial, or lumbosacral plexus can be caused by trauma, malignant infiltrative disease, vasculitis, infections (e.g. Lyme disease, HIV) or may be idiopathic (e.g. neuralgic amyotrophy, known as brachial neuritis or Parsonage–Turner syndrome when it involves the brachial plexus).

Diseases of the muscles may be primary (muscular dystrophies) or secondary (thyroid myopathy, drug-induced myopathy) in origin, be associated with metabolic disorders (e.g. glycogen storage diseases) or mitochondrial disorders (Kearns–Sayre syndrome, chronic progressive external ophthalmoplegia, MELAS syndrome), or be part of a systemic inflammatory disorder (polymyositis, dermatomyositis). Disorders of the neuromuscular junction may be antibody mediated (myasthenia gravis, Lambert–Eaton myasthenia syndrome (LEMS)) or toxin induced (botulism). The main anterior horn cell disorders are motor neuron disease (MND), poliomyelitis, and spinal muscular atrophy.

Context

The origin of weakness may be localized to upper motor neurons, lower motor neurons (including nerve roots, nerve plexuses, and peripheral nerves), anterior horn cells, neuromuscular junctions, or muscles. The upper motor neurons responsible for voluntary movement consists of the neurons located in the motor cortex and corticospinal (or pyramidal) tracts and their various connecting interneurons. The lower motor neurons originate in the anterior horn of the spinal cord. On leaving the spinal cord, the lower motor neurons become organized into plexuses (cervical, brachial, and lumbosacral), subsequently forming peripheral nerves which synapse with the muscle cell membrane at the neuromuscular junction. In the brainstem, the lower motor neurons in the cranial nerve motor nuclei innervate the muscles responsible for eye movements, speech, and swallowing.

Approach to diagnosis

Clinical history

The patient’s description of weakness must first be clarified and differentiated from malaise, lassitude, or fatigue, although fatigue itself is frequently present in neuromuscular diseases. A thorough history should include details of the onset and time course (acute, subacute, or chronic), pattern (e.g. generalized, hemiparetic, paraparetic, or monomelic; distal or proximal; symmetrical or asymmetrical; focal or multifocal), progression or worsening of symptoms, associated symptoms, past medical history, family history, drug history, travel history, and social history. Patients may volunteer examples of functional impairment

pointing towards a pattern of weakness; for example, difficulty rising from a chair or from squatting may indicate proximal muscle weakness, whereas difficulty opening jars or tripping may indicate distal weakness in the upper limbs.

A general medical evaluation should be done, with particular attention paid to respiratory and cardiovascular function, skin changes, thyroid function, skeletal deformities, and the presence of lymphadenopathy, fever, or weight loss.

Examination

Examination of the motor system should include an assessment of muscle bulk, tone, strength, reflexes, and gait. Other associated neurological features such as cranial nerve dysfunction, visual field detects, speech abnormalities, ataxia, sensory disturbance, and musculoskeletal deformities should be sought.

Muscle bulk

Atrophy with fasciculations may appear within a few weeks of onset of weakness caused by a polyneuropathy. Fasciculations may be localized in a radiculopathy. Muscle hypertrophy may be seen in some muscular dystrophies (e.g. pseudohypertrophy of the calf muscles, a classical finding).

Tone

Flaccid weakness point to a lower motor neuron disorder. However, acute upper motor neuron disorders can present with a flaccid weakness at onset. Hypertonia in upper motor neuron disorders appear days or weeks later, typically resulting in a ‘clasp-knife’ rigidity. Ankle clonus may be elicited in upper motor neuron disorders.

Strength

Muscle strength may be assessed manually by muscle resistance testing or by functional testing. Strength is usually graded using the 6-point BMRC (British Medical Research Council) scale (Table 44.1). Functional testing such as tiptoe and heel walking can be used to evaluate distal lower limb power, whereas the patient’s ability to stand from sitting unaided reflects proximal muscle power. Grip strength can be quantitatively assessed using a dynamometer.

Table 44.1 Strength grading using the 6-point BMRC (British Medical Research Council) scale

BMRC scale	Evaluation

0	No movement observed
1	Flicker or trace of movement observed
2	Active movement with gravity eliminated
3	Active movement against gravity
4	Active movement against resistance
5	Normal strength

Adapted from Medical Research Council Aids to the examination of the peripheral nervous system, Memorandum no. 45, Her Majesty's Stationery Office, London, 1981. Used with the permission of the Medical Research Council.

Typically but not always, pyramidal weakness of the upper limbs has a predilection for extensors over the flexor muscles, whereas in the lower limbs the flexors are weaker than the extensors. Testing for a pronator drift is useful for eliciting a mild pyramidal weakness.

Pattern and distribution of weakness

Table 44.2 summarizes the most common patterns of weakness which help localize the site of the lesion.

Table 44.2 Weakness patterns that help localize the site of the lesion

UMN or LMN signs	Distribution of weakness	Likely location of lesion
UMN	Hemiparesis Hemiparesis with cranial nerve deficits Tetraparesis Tetraparesis with cranial nerve deficits Paraparesis of the lower limbs	Contralateral cerebral hemisphere Brainstem Spinal cord (cervical) Brainstem Spinal cord (thoracic)
LMN	All four limbs, facial, ocular, and bulbar weakness	Neuromuscular junction Muscle (myopathy, dystrophy)

	All four limbs, predominantly proximal weakness All four limbs, predominantly distal weakness Facial, ocular, and bulbar Focal, asymmetric (single limb) Multifocal, asymmetric (more than one limb)	Peripheral nerves (peripheral neuropathy) Cranial nerves (cranial neuropathy) Nerve root (radiculopathy), plexus (plexopathy), or peripheral nerve (mononeuropathy) Peripheral nerves (multiple mononeuropathy)
Mixed UMN and LMN	All four limbs with bulbar and facial weakness but no ocular involvement Paraparesis of the lower limbs	Anterior horn cell Conus medullaris

Abbreviations: LMN, lower motor neuron; UMN, upper motor neuron.

Reflexes

Tendon reflexes are diminished or absent in lower motor neuron disorders and exaggerated in upper motor neuron disorders. In lower motor neuron disorders, the distribution of the diminished reflexes can help to localize the lesion. For instance, a diminished/absent ankle jerk could indicate a lesion of the S1 nerve root or the sciatic nerve on the same side.

A spinal cord lesion may cause tendon reflexes to be diminished at the level of the lesion, but exaggerated below it. The plantar response is typically extensor in upper motor neuron disorders.

Tendon reflexes are preserved in myasthenia gravis (MG) and botulism but are reduced or absent in LEMS. In LEMS, facilitation of reflexes (appearance after repeated muscle contraction) is characteristic.

Tendon reflexes may be preserved or reduced in myopathies.

Gait

A waddling gait is typical of proximal muscle weakness. A high-stepping gait is seen in ankle dorsiflexion weakness (foot drop). A scissoring gait, caused by a tendency to adduct both hips, occurs in a spastic paraparesis.

Specific clues to the diagnosis

Symptom onset and time course

Sudden onset of weakness without warning is suggestive of a vascular cause such as an ischaemic or haemorrhagic stroke.

Subacute onset over days is typical of GBS, vasculitic neuropathy, polymyositis, and acute CNS demyelination (e.g. multiple sclerosis, inflammatory myelitis).

A more insidious onset with progressive symptoms over weeks to months is seen in space-occupying lesions such as tumours and vascular malformations, neurodegenerative conditions such as MND, neurosarcoidosis, and many peripheral nerve diseases. Progression over years can be seen in certain muscular dystrophies.

Fluctuating weakness is characteristic of MG and mitochondrial and metabolic muscle disorders, where it is precipitated by activity.

Weakness caused by vasculitis, chronic inflammatory demyelinating radiculoneuropathy (CIDP), multiple sclerosis (MS), or porphyria may demonstrate a relapsing pattern.

A childhood history of poor motor skills or slow development point towards a hereditary or genetic cause of weakness, such as hereditary spastic paraparesis, muscular dystrophy, and various forms of CMT.

Involvement of the motor system only

Sensory signs are absent in myopathies, neuromuscular junction disorders, pure motor neuropathies, and anterior horn cell disease (e.g. MND), although some patients may complain of mild sensory symptoms. A pure motor neuropathy should be differentiated from MND. Variants of GBS, lead toxicity, and a subtype of CMT may present with a pure motor neuropathy.

Involvement of the sensory system

In upper motor neurons, sensory signs may be seen in cerebral, brainstem, and spinal cord lesions. In lower motor neurons, sensory signs are present in peripheral nerve disorders, including radiculopathies, plexopathies, mononeuropathies, and the various causes of polyneuropathies.

Involvement of the autonomic nervous system

Autonomic disturbance (e.g. orthostatic hypotension, cardiac arrhythmias, pupillary dysfunction, urinary retention) is often present in some polyneuropathies (e.g. in GBS, amyloidosis, and diabetes), LEMs, and botulism.

Involvement of the cranial muscles

An upper motor neuron pattern of facial weakness (forehead sparing) is seen in brainstem lesions of various causes. A lower motor neuron pattern of facial weakness is seen in vasculitis, neurosarcoidosis, Lyme disease, GBS, MG, botulism, HIV infection, myotonic dystrophy, mitochondrial myopathies, the fascioscapulohumeral and oculopharyngeal forms of muscular dystrophy, and idiopathic Bell's palsy.

Bulbar weakness causing dysarthria and dysphagia occurs in brainstem lesions, MND, GBS, MG, botulism, myotonic dystrophy, muscular dystrophy (oculopharyngeal form), thyroid myopathy, and inflammatory myopathies. Wasting and fasciculations of the tongue raises a strong suspicion of MND.

Weakness of the extraocular muscles giving rise to an ophthalmoplegia may be present in brainstem disorders, variants of GBS (e.g. Miller Fisher syndrome), MG, botulism, mitochondrial myopathies, and the oculopharyngeal form of muscular dystrophy.

Involvement of the sphincter muscles

Sphincteric disturbance (urinary retention and loss of anal tone) with a sensory level is highly suggestive of a spinal cord lesion.

Sphincteric disturbance with 'saddle' anaesthesia and lower limb weakness is suggestive of a lesion of the conus medullaris or cauda equina. Conus medullaris lesions tend to present with bilateral mixed upper motor neuron and lower motor neuron signs (brisk knee jerks and absent ankle jerks, occasionally with fasciculations) whereas cauda equina lesions present with lower motor neuron signs which are often unilateral or bilateral and asymmetrical.

Involvement of the respiratory system

Neuromuscular disorders may present with respiratory dysfunction due to diaphragmatic and respiratory muscle weakness. Symptoms include dyspnoea, orthopnoea, and morning headaches and, if severe, may result in respiratory arrest. Acute onset of respiratory failure is seen in GBS, MG, and botulism, whereas a gradual, progressive worsening is seen in MND and the muscular dystrophies (Duchenne, myotonic dystrophy, and limb-girdle forms).

Damage to the spinal cord may result in diaphragmatic weakness (C3–C5) and intercostal muscle weakness (T1–T11).

Respiratory muscle function may be assessed at the bedside by asking the patient to cough or sniff (diaphragmatic function), observing for paradoxical abdominal movements on inspiration, and measuring their forced vital capacity (FVC). Elective intubation should be considered if FVC falls below 15 ml/kg.

Lesions of the brainstem can adversely affect respiratory function through depression of the respiratory drive.

Other signs and symptoms

Muscle pain or myalgia can occur in an inflammatory myopathy and myotonic dystrophy. Neuropathic pain often occurs with a vasculitic neuropathy, radiculopathy, and compressive neuropathy. Shoulder pain is usually present in brachial neuritis. Back pain is a typical feature of cord compression but may also appear in GBS.

Myotonia is the slow relaxation of skeletal muscle after contraction (e.g. with handgrip), typically seen in myotonic dystrophy. Other features characteristic of this condition include frontal balding and temporalis wasting (myotonic facies), cataracts, cardiac arrhythmias, and cardiomyopathy

Muscle cramps and exercise intolerance may indicate a metabolic myopathy, mitochondrial myopathy, or a myotonic dystrophy.

Trophic changes may be present in peripheral nerve disorders. A skin rash is often a hallmark of a vasculitic process or may be associated with a connective tissue disorder.

Drug and social history

Chronic alcoholism and malabsorption syndromes predispose to subacute combined degeneration of the spinal cord (vitamin B_{12} deficiency) and a thiamine deficiency-related sensory–motor neuropathy. Injecting drugs users are at risk of botulism and embolic strokes. Patients on statins or steroids can rarely suffer from a drug-induced myopathy. Certain cytotoxic chemotherapy drugs (e.g. vinca alkaloids) can be associated with a sensory–motor peripheral neuropathy.

Key diagnostic tests

Medical imaging

CT is useful in the emergency setting, such as when an intra-cerebral bleed, ischaemic stroke, solid tumour, or acute cord compression is suspected to be the cause of weakness. Magnetic resonance imaging, however, is preferable over CT as a diagnostic aid due to the superior image resolution and sensitivity to soft tissue pathology. The finding of weakness with a possible upper motor neuron origin or weakness affecting the cranial muscles should prompt an MRI of the relevant segment of the neuroaxis. MRI is also useful in demonstrating nerve root impingement in radiculopathies, inflammation, or compression in plexopathies and to identify subclinical changes or the pattern of affected muscles in myopathies.

CSF analysis

Barring contraindications to lumbar puncture, CSF analysis may be undertaken to aid the diagnosis of an inflammatory, infective, or malignant cause of weakness affecting the central nervous system or spinal roots. In the context of weakness, raised CSF protein is seen in infections, intra-cerebral haemorrhage, malignant infiltration, and inflammatory disorders such as GBS, CIDP, and MS. Oligoclonal bands have a relatively high specificity for MS, although they may also be present in vasculitis of the CNS, neurosarcoidosis, Lyme disease, and viral infections.

Neurophysiological studies

Electromyography (EMG) may aid in the differentiation between weakness of a neuropathic cause or a myopathic origin and can assist in localizing the lesion in a plexopathies, radiculopathies, or mononeuropathies. Findings in MND characteristically reflect denervation (fibrillation potentials, giant motor unit potentials, and positive sharp waves) and reinnervation changes (increased jitter). Myopathies typically demonstrate spontaneous activity with fibrillations, positive sharp waves, and low-amplitude polyphasic action potentials of a short duration.

Nerve conduction studies can differentiate axonal from demyelinating peripheral neuropathies. In demyelination, distal motor latency is prolonged and motor conduction velocity is slowed. In axonal neuropathies, the compound muscle action potential is reduced but the distal motor latency and conduction velocity can be preserved. In nerve entrapment, there is slowing of nerve conduction at the site of compression.

Repetitive nerve stimulation is performed in suspected myasthenic syndromes, showing characteristic decrement in the compound muscle action potential in MG and an increment in LEMS.

Somatosensory, visual, and brainstem auditory evoked potentials are useful in the assessment of CNS conduction, particularly in cases of suspected MS.

Nerve and muscle biopsy

Peripheral nerve biopsy (usually sural or radial nerve) is indicated where a vasculitic or neoplastic cause of a peripheral neuropathy is suspected. Muscle biopsy (usually quadriceps) is performed in cases of suspected myositis, muscular dystrophy, and mitochondrial and metabolic myopathies, aided by immunostaining and electron microscopy.

Other diagnostic tests

In generalized polyneuropathies, tests that need to be considered include antiganglioside antibodies (in suspected GBS), thyroid function, fasting blood glucose, vitamins A, E, and B_{12}, erythrocyte

sedimentation rate, antinuclear antibodies (ANA), antineutrophil cytoplasmic antibody (ANCA), serum electrophoresis, and serum angiotensin-converting enzyme (ACE).

Creatine kinase (CK) is released by muscles during breakdown. CK levels are raised in inflammatory and immune myopathies, Duchenne dystrophy, and Becker dystrophy. However, CK may also be increased in Afro-Caribbeans in the absence of pathology. Trauma, sepsis, or exercise can also increase CK levels.

Tests for metabolic and mitochondrial myopathies include serum and CSF lactate, urinary organic acids, and serum and urine carnitine levels.

In MG, anti-acetylcholine antibodies and/or muscle-specific kinase (MuSK) antibodies may be present. To aid in the diagnosis further, an edrophonium test can be performed, consisting of an intravenous bolus injection of edrophonium, a short-acting acetyl-cholinesterase inhibitor, which causes a brief but marked improvement of symptoms in patients with the condition.

Paraneoplastic causes of weakness are very rare and can take the form of a myelitis, motor neuropathy, myopathy, or a neuromuscular junction disorder. The underlying pathogenesis is believed to be autoimmune. However, in most cases, an antibody is not identified. Voltage-gated calcium channel antibodies are associated with LEMS, a neuromuscular junction disorder which may present as a paraneoplastic syndrome. A skeletal survey, chest and abdominal CT, or whole-body PET may help localize a malignancy in a suspected paraneoplastic syndrome.

Genetic tests are conducted in suspected hereditary neuropathies and myopathies, usually guided by the history, examination, and clinical findings. Techniques include cytogenetics, DNA mutation tests, and microarrays.

Introduction to therapy

Therapy is tailored to treating the underlying cause of weakness and symptoms that arise from it. Neurosurgical intervention may be sought for compressive or space-occupying lesions of the brain and spinal cord. Therapy for ischaemic stroke comprises of antiplatelet therapy, anticoagulation therapy, thrombolytic therapy (where indicated), secondary prevention, and neurorehabilitation. Disease activity in inflammatory and immune-mediated conditions may be controlled by steroids and/or immunosuppressants. Malignant tumours may be treated with surgical debulking, radiotherapy, and/or chemotherapy, depending on tumour type and location.

Supportive therapy in the form of mechanical ventilation may be required for patients with respiratory muscle weakness. Enteral feeding via a gastrostomy or jejunostomy should be considered in those with bulbar weakness who are at risk of aspiration. Skeletal muscle relaxants (such as baclofen and tizanidine) are used to treat spasticity and recurrent muscle spasms. Regular Botox injections can help relieve spasticity and dystonias. Further supportive care is provided by physiotherapists and occupational therapists.

Specific treatments

GBS is treated with intravenous immunoglobulin (IVIg) typically at a dose of 0.4 g/kg day^{-1} for 5 days, or plasma exchange. Therapy is generally indicated if the patient is no longer able to walk. IVIg is preferred over plasma exchange, as it is much easier to administer. Patients require regular monitoring of their respiratory function (FVC) and cardiovascular function (cardiac rhythm and blood pressure).

CIDP can be treated with long-term corticosteroids, intravenous immunoglobulins, or plasma exchange. In patients who cannot have the aforementioned therapy or fail to respond adequately to them, immunosuppressive therapy (such as azathioprine and mycophenolate mofetil) may be considered.

Treatment for MND is largely supportive and consists of physiotherapy, occupational therapy, nutritional support, respiratory support, and social support. Riluzole 50 mg orally twice a day may extend survival modestly, although it has not been shown to improve strength or quality of life.

Treatment strategies for MG depend on the severity of symptoms, the age of the patient, the presence of a thymoma, and other related comorbidities. Patients with mild symptoms may require only symptomatic therapy with an anticholinesterase drug (i.e. pyridostigmine). For those who remain symptomatic on anticholinesterases or have more generalized weakness, treatment with corticosteroids is usually initiated along with bone and gastric protection. Immunosuppressive therapy (e.g. azathioprine) is often used as a steroid-sparing agent and for those who do not adequately respond to pyridostigmine and steroids. Thymectomy may be considered in

seropositive patients under 60 years of age, and in all patients with thymoma. In a myasthenic crisis, plasma exchange or IVIg is used as acute therapy.

Treatment for MS is predominantly with immunomodulatory drugs such as glatiramer acetate, interferon beta, and natalizumab, which aim to reduce relapse rates. High-dose corticosteroids are used in the management of acute relapses to aid in the recovery rate.

No specific therapy is available for the majority of the hereditary and metabolic neuromuscular disorders. Treatment is supportive.

Prognosis

Prognosis largely depends on the cause of the motor weakness, treatment, and the presence/absence of complicating factors. In many causes of neuromuscular weakness, prognosis is poorer in patients who have cardiorespiratory involvement and in those who acquire the disease at an older age. Nonetheless, the prognosis for many such disorders has vastly improved with the use of ventilatory support, cardiac intervention, antibiotics, and immunosuppressive and immune-modulatory treatments. Prognostic factors for specific conditions are discussed as follows.

Poorer prognosis in GBS is associated with older age, ventilator dependency, campylobacter infection, and axonal neuropathy. Mortality is as high as 8%. One-third of patients have significant residual disability despite treatment.

The vast majority of CIDP patients (90%) respond well to therapy. However, at least 50% relapse within 4 years, and less than a third achieve remission off treatment.

The prognosis of MND remains very poor. Mean survival time from diagnosis is 2 years in the classical form. Prognosis is worse in patients who are older and those with a rapid decline following initial diagnosis.

Poor prognostic factors in MS include older age of onset, male sex, progressive course at onset, early residual disability, short inter-relapse interval, and high early relapse rates. The majority of patients with relapsing–remitting MS eventually demonstrate secondary progression.

How to handle uncertainty in the diagnosis of this symptom

Not infrequently, investigative test results do not correlate with the clinical examination findings of weakness. The approach to this issue is to retake the clinical history and carefully re-examine the patient, either noting any inconsistencies or confirming one’s earlier findings. Neurological signs and symptoms have a tendency to evolve over a period of time, often becoming clearer or more distinct as the illness progresses.

Tests results including imaging findings should be re-evaluated in the correct context. Diagnostic tests performed too early or in mild disease states may yield normal results. Examples include the frequent finding of a normal CT scan in an acute stroke, and normal cerebrospinal fluid markers with normal electrophysiological readings in early GBS.

Alternative diagnoses are often worth considering. Migraines and epilepsy can present with episodes of brief motor dysfunction which can mimic TIAs or strokes. In the elderly, fractures and joint dislocation may present with painless loss of limb function.

Non-neurological or non-organic muscle weakness is commonly encountered in the clinical setting. This could be considered if inconsistencies are demonstrated in the history, and examination findings with the clear presence of strong indicators of a somatization disorder in the patient's past medical history (which is usually notable for abnormal illness behaviour), their social history (substance abuse and self-harm are often evident,) and their mental state (frequently coexisting depression, anxiety, or a personality disorder).

Further Reading

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