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Motor Neuron Disease: To Identify the Mimics and Chameleons at the Early Stage

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ABSTRACT

Motor neuron disease is a devastating progressive neurodegenerative disease, which is irreversible. Delay in the diagnosis is the norm among neurologists and other medical practitioners. It can affect both central and peripheral nervous systems. It also manifests by upper neuron, lower motor neuron signs or a mix of the above two and can affect the bulbar system. Because the disease is primary progressive, it mimics many other neurological deficits at different stages. Unfortunately, there is no one test to confirm the diagnosis at the early stage, typically during the first 12 months. Probably, all the differential diagnosis that reversible and treatable should be ruled out specifically. Patient may be referred to different specialities before being referred to general neurologist. Furthermore, general neurologist may need to refer the patient to motor neuron specialist; motor neuron specialist would like to make sure that he eliminated all the mimics before breaking the bad news with the patient and family that the motor neuron disease is the most probable diagnosis. It is of paramount important that the patient received the diagnosis as early as possible so he/she can benefit from multidisciplinary and interdisciplinary care team and to alleviate his/her symptoms and also to arrange advanced care planning, and assessment of ceiling of the goals of the care. It is of note that currently, patient may benefit from assisting dying if he/she fulfills the criteria. This review aims to include most common mimics and chameleons in the clinical practice and to discuss the diagnostic tools that should be performed for those who has been considered possible motor neuron disease. And to discuss the avenue for assessment by multidisciplinary care team which includes general neurologist, motor neuron specialist, respiratory physician, gastroenterologist, psychologist and psychiatrist, general physician, and allied health.

Keywords

Motor Neuron Disease, HIV, Biomarkers, Autoimmune diseases, Myasthenia gravis.

Introduction

One of the hardest tasks for neurologist is to break the news to patients who are newly diagnosed motor neuron disease, as it is an irreversible and progressive condition with invariably has a fatal outcome that brings significant distress to patients and their family. To avoid the diagnostic delay is very difficult as there is no one diagnostic test for MND and the quest for biomarkers is ongoing, and the clinical presentation may not be manifested with all signs at one time [1]. The patient with pure upper motor neuron may develop slowly progressive lower motor neuron signs and the same for lower motor neuron disease, extraocular muscles, sphincters and gross sensory signs are red flags for pure motor neuron disease, and inappropriate referrals to other subspecialities are very common. The pre-symptomatic phase may take years to develop clinical signs that drive patients to seek medical help. However, in the most common scenarios, given the uncertainty of the clinical picture, it may take 2-12 months before GP could start to consider MND as a possible differential diagnosis and refer the patient to general neurologist. A further delay from general neurologist to MND specialist may take up to 4 months. Therefore, the interval between a possible patient initially seeking medical advice and eventually being confirmed as MND is ranging 4-16 months (Figure 1) [2].

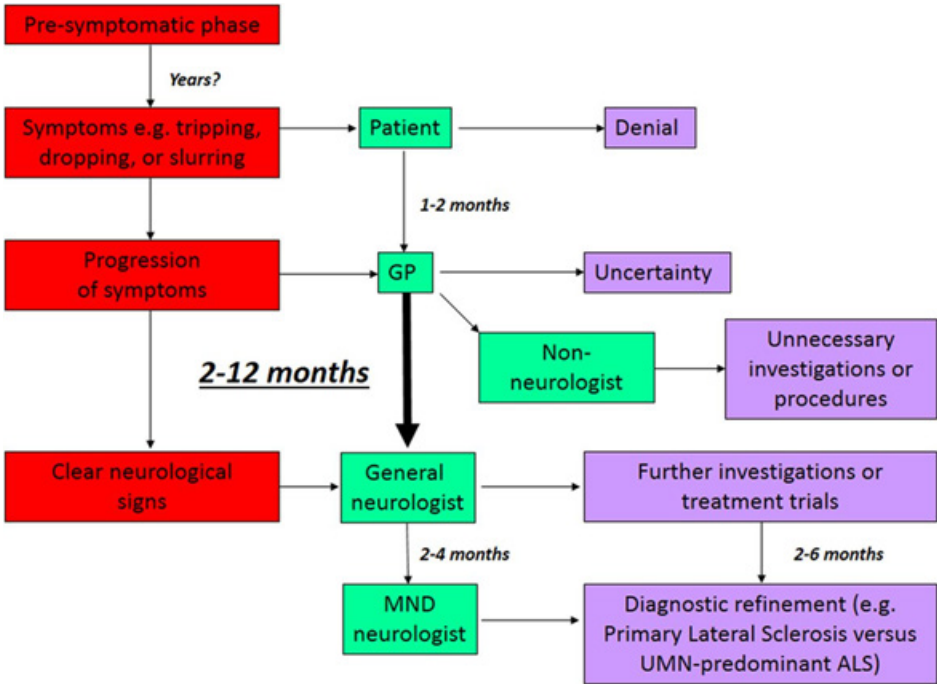

Figure 1: The diagnostic timeframe and common causes of delay in MND.

The diagnosis of MND is clinical, although usually supported by investigations such as electromyography and nerve conduction studies (EMG/NCS), imaging and blood work [3-5]. It can present with both upper and lower motor neuron disease like amyotrophic lateral sclerosis which accounts up to 85% of motor neuron disease, pure lower motor neuron (primary muscular atrophy) account for 6%, and pure upper motor neuron disease only (primary lateral sclerosis) accounting for 2% [6,7]. The variability of onset and clinical features may mimic other neurological conditions in different stage of progression. This review summaries those non-MND reversable conditions that easily to be missed but need to be considered or ruled out before confirming the diagnosis of MND, and the suggestive investigations or tools to differentiate in the clinical practice.

Upper Motor Neuron Symptoms

Primary Progressive Multiple Sclerosis

About 10–15% of patients with multiple sclerosis (MS) present with gradually increasing neurological disability which is known as primary-progressive multiple sclerosis (PPMS) [8]. The atrophy and intrinsic abnormalities in the intercranial grey and white matter and in spinal cord correspond to the usual clinical presentation of progressive spastic paraplegia. According to 2017 McDonald criteria, there should be at least one MS-like lesion in the brain and at least two lesions in the spinal cord and positive test for oligoclonal bands in the CSF [9].

Lower Motor Neuron Symptoms

Multifocal Motor Neuropathy with Conduction Block

Immune mediated asymmetrical motor neuropathy affecting the upper limbs more than lower limbs, Serum IgM, anti-GM1 are usually positive, disease has favourable response to intravenous immunoglobulin. Nerve conduction and EMG are diagnostic show reduction in the compound muscle action potential, and conduction blocks not (on known entrapment sites), prolonged motor nerve latencies, slow conduction velocity, F wave may be absent, EMG usually show reduced recruitment of muscle unit action potentials, and CSF protein usually normal which differentiates it from motor dominant chronic inflammatory demyelinating peripheral neuropathy [10].

Miller Fisher syndrome

Miller Fisher syndrome (MFS) is a rare, acquired nerve disease related to Guillain-Barre syndrome causing dysfunction of the 3rd, 4th and 6th cranial nerves, confusion, ataxia, areflexia and nystagmus. The principal autoantibody is directed against ganglioside GQ1b, which is present in the blood of at least 80% of people with MFS, therefore can be used to confirm the diagnosis. Electromyography and nerve conduct study are often done to support the diagnosis. MFS can also related to the previous infection with campylobacter, cytomegalovirus, Epstein–Barr virus, HIV is common [11].

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

CIDP can be predominantly presented with motor neuron system impairment. Symmetrical affecting proximal and distal muscles, face and neck muscles could be involved, autonomic and respiratory muscles are relatively spared, muscles stretch reflexes are usually depressed or absent with flexor planters. CSF protein is elevated, and the fluid is a cellular, unmatched oligoclonal band is detectable in 60% of patients. Nerve conduction study is characterised by demyelination, slow motor nerve conduction velocities, prolonged distal latency, delayed F-waves, motor conduction block, abnormal temporal dispersion in the form of prolongation of proximal motor response duration by 40%. Steroid, plasmapheresis and immunoglobulin are considered first line treatment with variable response [12].

Lyme Neuroborreliosis

The clinical presentation of Lyme neuroborreliosis (LNB) can vary widely, partly due to the genetic differences in spirochetal strains [13]. The most common neurological manifestation of LNB in adults is the Bannwarth syndrome with painful radiculoneuritis and aseptic meningitis [14]. About 80% of cranial nerve involvement in LNB affect fascial nerves, bilaterally in 25% of the cases [15,16]. Apart from Bannwarth syndrome, plexus neuritis or mononeuritis multiplex are other peripheral manifestations which can be seen in 5-10% of LNB cases [17]. Serology is diagnostic and treatment is curative.

Cervical Polyradiculopathy

Sensation abnormality and motor deficits are the most common features of cervical polyradiculopathy due to disc degeneration. Mostly it presented unilaterally and radiating to the ipsilateral arm in dermatomal distribution. Its commonly affect spine on the levels of C5, C6, C7, C8, T1. MRI can demonstrate diagnostic structural abnormality, while EMG and NCS are usually used to confirm the diagnosis and to differentiate from entrapment neuropathy. Symptoms usually improve with physiotherapy, focal steroid injection and surgical intervention [18,19].

Radiation-Induced Radiculopathy

Radiotherapy to the patients with testicular or gynaecological malignancy might leads to clinical pattern of motor neuron impairment at the level of lower spinal cord with no sensory involvement, brachial plexopathy due to radiotherapy of the breast and neck are not uncommon. The latency to clinical manifestation may take up to 30 years to be clinically visible. diagnosis usually relay on the medical history and not investigation [20].

Myoneural Junction Disorder

Myasthenia Gravis

Generalised myasthenia is a fluctuating myoneural junction disease causing weakness in the later of the day, unlikely to cause muscle wasting, stretch reflexes are preserved, and sensations are spared. It can cause severe respiratory failure and death if the respiratory muscles are involved. It can be exacerbated by infection, gentamycin, fluoroquinolone, betablockers, neuromuscular blocking agents, bulbar muscles can be involved resulting difficulty in swallowing and speech, hoarseness of voice and dysarthria. The involvement of face muscles can cause expressionless face and dropped head; proximal muscles are affected more than distal, thymic enlargement and thymoma are not uncommon. Other autoimmune disease like Gravis Disease, type 1 diabetes, Celiac disease should be ruled out as organ specific autoimmune diseases are common in myasthenia gravis.

Acetylcholine receptor antibodies are positive in almost 70% of patients with generalised myasthenia. Anti-MUCK antibodies can be detected in 10% of patients and become less responsive to treatment. 40% of seronegative generalised myasthenia could be positive for antiLRP4 antibodies, antistriated muscle antibodies are positive in 50% of patients with Thymoma. Repetitive nerve stimulation and single fibre stimulation EMG are diagnostic methods as they cause low excitatory post synaptic potential and jitter respectively.

Ocular myasthenia is unlikely to be the differential diagnosis as extraocular muscles involvement is an exclusion criterion for diagnosis of motor neuron disease [21].

Muscular Disorder Symptoms

Spinobulbar Muscular Atrophy (Kennedy Disease)

it is an x-linked recessive disease, male patient manifested with sever disease than females, impaired glucose tolerance and elevated lactic acid are common due to associated mitochondrial dysfunction. This is a genetic disease common in males characterised by spinal and bulbar muscles weakness causing difficulty of walking, recurrent falls, bulbar muscle weakness caused difficulty of swallowing and speech, gynecomastia and infertility are due to incomplete androgen insensitivity syndrome, generalised fasciculation are common [22,23].

Inclusion-Body Myositis

It is one of the most common acquired idiopathic inflammatory myopathies in individuals over the age of 50 [24]. It is a late onset treatment-refractory autoimmune disease of skeletal muscle associated with a serum autoantibody (anti-cN1A), an HLA autoimmune haplotype, and muscle pathology characterized by cytotoxic CD8+ T cell destruction of myofibers. It could be manifested by selective involvement of finger flexors and quadriceps muscles. Missed diagnosis are very common as polymyositis or arthritis, but not uncommonly associated with cardiac and other autoimmune diseases. It is a disease which is difficult to treat and excluding another differential are very important, especially if they are treatable [25].

Poliomyelitis

Poliomyelitis now has become much less common, however, causes acute progressive motor neuron disease due to anterior corn cell injury. It is characterised by weakness wasting and fasciculation, with no sensory involvement. When acute flaccid weakness is a dominant part of the clinical presentation, suggested testing includes blood, cerebrospinal fluid (CSF), stool, and respiratory tract specimens. The sensory involvement is a red flag to exclude HIV [26].

Syringomyelia/Syringobulbia

Syringomyelia is a rare condition affecting the spinal cord. It commonly causes wasting, fasciculation and dissociated sensory loss. 10% of MND may have sensory impairment involvement; therefore, the syringomyelia/syringobulbia can be considered a differential in the differential diagnosis if sensation were spared. Otherwise, for those more common MND without sensory change should exclude syringomyelia/syringobulbia without sensation impairment. However, syringomyelia usually involve both motor neuron and sensory neuron and can be identified by spine MRI clearly [27,28].

Mix of Upper and Lower Motor Neuron Disorders

Subacute Combined Degeneration of the Cord

It usually affected patients with with B12 deficiency, copper deficiency, inhaled nitric oxide toxicity, bariatric surgery, and recent gastric sleeve surgery. Discriminating signs are peripheral neuropathy, papilledema, spinal-cerebellar ataxia. The MRI usually showed high signal in the posterior cervical cord. Failure to identify the neurological deficit in timely manner will result in fixed neurological deficiency [29].

Syphilitic taboparesis

Taboparesis is a condition in late neurosyphilis, which usually affected central and peripheral nervous system. The manifestation usually appears many years after syphilis infection, which is due to chronic meningoencephalitis and general baresis of insane resulting in multiple strokes, vascular dementia, and lancinating limb pain. Supporting signs include depression, delirium, mania, and result in psychosis. Classically patients have ataxia, lancinating limb pain, pains, bladder dysfunction, paraesthesia, and vision changes. Additional neurologic deficits include pupillary abnormalities (Argyll Robertson pupils), ocular palsies, diminished stretch reflexes, vibratory and proprioceptive impairments, ocular palsies, and Charcot joints [30-32]. CSF analysis is recommended, CSF VDRL is highly specific and is generally accepted as the diagnostic test. CSF treponemal tests (FTA-ABS) and CSL pleocytosis are highly sensitive but is nonspecific [30]. Neuroimaging can be helpful in the diagnosis. The most common findings are frontal and temporoparietal atrophy [30,33].

Friedlreich's Ataxia

Friedreich's ataxia is a relatively rare inherited condition of the nervous system characterised by the gradual loss of coordination. Although a typical age of onset between 10 and 15 years, it can be as late as middle age. In addition to neuropathological disabilities such as ataxia, sensory loss, and muscle weakness, common signs are scoliosis, foot deformity, and hypertrophic cardiomyopathy. Approximately 10 % of patients with Friedreich's ataxia develop diabetes [34].

Pellagra Neuropathy

Pellagra is a systemic disease caused by a severe deficiency of niacin (vitamin B3) which leads to systemic disease with clinical manifestations from the skin, gastrointestinal tract and the nervous system [35]. The disease is now rare due to the widespread consumption of bread enriched with niacin, but can still be encountered in alcoholics, individuals with malabsorption from GI diseases or concurrent use of medications that interfere with the production of niacin from tryptophan, such as isoniazid, azathioprine, and some chemotherapy agents [36]. The neurological syndrome of pellagra is not well defined. Reported cases, especially of patients with alcoholic pellagra are quite rare [37].

Most patients will not present with the whole spectrum of manifestations as before (Diarrhia, dementia, death).

Movement Disorder

Parkinson's plus Syndromes

Parkinson's plus syndromes (PPS), also called "atypical Parkinson's" is a neurovegetative disease characterised by bradykinesia, extrapyramidal rigidity, rest tremor and autonomic neuropathy and postural instability, the three common syndromes are supranuclear palsy, corticobasel degeneration and multiple system atrophy [38-40].

Systemic Non-Specific Symptoms

Neurologic Amyotrophy

A common inflammatory disease affects long thoracic, suprascapular, superficial radial, anterior interosseous, brachial plexus, and phrenic nerves, onset is acute, MRI with gadolinium and high-resolution magnetic resonance neurography are used as a diagnostic investigation. Treatment is usually symptomatic management, methylprednisolone and immunoglobulin help recovery, more than 60% of cases will have residual symptoms [41,42].

Benign Fasciculations

Benign fasciculation is characterised by being focal or multifocal, intermittent, associated with fatigue, tiredness, anxiety, thyrotoxicosis, cervical spondylosis, chronic use of steroid. Muscular ultrasound has been proved to be more sensitive than specific than EMG. Clinical detailed history is very important to rule in benign fasciculations [43].

Chronic Lead Poisoning and Porphyria

Chronic lead poisoning can lead to motor neuropathy, basophilic stippling, increased urinary metanephrines, and coproporphyrins. chronic lead poisoning can be confirmed by history of lead exposure and high blood lead level, however, it is essential to rule out alterative conditions by performing full blood count, inflammatory markers, full biochemistry including creatinine kinase, immunoglobulin, serum and protein electrophoresis, flu cytometry to exclude B and T cell monoclonality, thyroid function and metabolic panel including B12, serum copper, calcium and phosphate, septic screen, celiac screen, Pan CT to exclude malignancy, HIV and Lyme serology, long chain fatty acids and genetic for adrenoleukodystrophy, FDG-PET scan. Other specific neurological investigation including MRI of the brain and spine, CSF study for cells, proteins, monoclonal band, EMG and nerve conduction study need to be considered. It should not stress much on vitality of very early neuron disease and exclusion of other mimics as it gives the patient a golden chance to be cared by a multidisciplinary team (MDT), including neurologist, respiratory physician, psychologist, chronic pain service, gastroenterologist, physiotherapist, palliative care service, speech pathologist, neuropsychiatrist, to improve spasticity, pain, cramps, dyspnoea, bronchial secretion, dysphagia, dysarthria, depression, sleep disorder, fatigue, respiratory dysfunction, bulbar symptoms, diaphragmatic symptoms, fatigue, communication, orthopnoea, deep vein thrombosis, skin care, nutrition hydration, equipment and services to support mobility, cognition, behavioural issues, mood. The residential care and advance care planning should

be considered to guide the family and healthcare professionals to provide the most appropriate care respecting patients' wishes to maintain their quality of life. The end-of-life care may also include the discussion of celling of management, terminal care and after care including bereavement, counselling and social work involvement [44,45].

Inherited Background

Hereditary Spastic Paraplegia (HSP)

As a neurodegenerative disease, HSP affects corticospinal and posterior column. It may cause spastic paraplegia, hyperreflexia, overactive bladder, bilateral extensor plantar, unstable gait, and muscles fragility [46], most commonly autosomal dominant and less commonly autosomal recessive, X linked recessive and mitochondrial, vibrion and sense of position often impaired, and Romberg sign often positive. Other uncommon associations are seizures, muscles wasting, ataxia, peripheral neuropathy, intellectual disability, extrapyramidal syndrome, Dubuytren contracture, varicose veins, and gastro oesophageal reflux [47].

X-linked Adrenoleukodystrophy

X-linked Adrenoleukodystrophy is a peroxisomal disorder caused by mutations in the adenosine triphosphate (ATP)-binding cassette (ABC), subfamily D, member 1 gene (ABCD1), located at Xq28, that encodes an ABC transporter [48]. It can present with primary adrenal insufficiency due to accumulation of long-chain fatty acids in the adrenal gland and white matter of the brain and spinal cord causing myelopathy, and chronic brain syndrome. The early diagnosis is of paramount importance as bone marrow transplant is curative [49,50].

Conclusion

Motor neurone disease initially identified as a clinical diagnosis. Given the non-reversable trajectory, confirmation of the disease should be carefully considered by excluding all the other treatable mimics and chameleons. EMG, nerve conduction study, CSF and blood testing and images are complementary for the early diagnosis. It is vital as it gives the prognostication of life expectancy to patients and families, and health care professionals particularly in a setting of progressive incurable illness. Series of vital health care decisions including advance care planning, discharge planning, personal finance, hospice referral are dependent on expected survival duration. Early diagnosis of motor neuron disease with the involvement of MDT is not only important to improve the surviving time but also for prolongation the period of good quality-of-life by maintaining independence, prevent complication and provide patient with dignity in life and death.

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