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A Review on Effect of Physical Activity as an Exogenous Factor and Cognitive Change in Motor Neuron Disease

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ABSTRACT

Motor neuron disease (MND) is a terrible neurodegenerative illness with a poor prognosis and significant impairment. Despite recent advances in symptomatic care, there are few medicines that can affect survival. However, a better understanding of the underlying etiology would substantially aid the task of finding effective treatments. In the etiology of MND, many potential external risk factors have been hypothesized as part of a gene-environment interaction. Following reports of a greater than predicted incidence of MND in professional athletes, there has been an increasing interest in the role of intensive physical exercise in the development of the disease. Current hypotheses about the cellular and genetic causes of MND also support this conclusion. Epidemiological evidence, on the other hand, is contradictory and inconclusive. FTD/motor neuron disease is the name given to a motor neuronopathy that complicates frontotemporal dementia (FTD) (MND). FTD is marked by severe personality changes, abnormal social behavior, and executive difficulties caused by frontal and temporal neocortical atrophy. Bulbar palsy and limb amyotrophy are symptoms of motor neuron disease. Micro vacuolation of the cerebral cortex is the most common histological alteration, along with atrophy of the bulbar neurons and anterior horn cells of the spinal cord. Large pyramidal cortical neurons, surviving cranial nerve nuclei, and anterior horn cells all have ubiquitinated inclusion bodies. Evidence is accumulating that some patients with classical MND/amyotrophic lateral sclerosis (ALS) who are not regarded to be demented show frontal executive function abnormalities. Moreover, frontal lobe abnormalities have been demonstrated by neuroimaging.

Keywords: MND, FTD, ALS, motor neuron, behavior, physical activity, cognitive change.

INTRODUCTION

"The gradual degeneration of upper and lower motor neurons is known as motor neuron disease (MND). In 1874, Jean-Martin Charcot coined the term "amyotrophic lateral sclerosis" to describe the condition (ALS). ALS is currently a name that describes the most common type of the disease and is frequently used interchangeably with MND." [1]

"Amyotrophic lateral sclerosis (ALS) is characterized by muscle atrophy or

weakening in one or more limbs or bulbar areas." [2] Pervasive muscular weakness develops as a result of a mix of upper and lower motor neuron failure. MND onset age, place of onset, and pace of progression are all extremely varied, with each of these characteristics playing a substantial effect in predicting life expectancy". [1] "It usually appears in the fifth decade of life, with a median survival time of four years after diagnosis. MND is the third most common neurological degenerative ailment after Alzheimer's and Parkinson's diseases, with an incidence of 2/100,000," [3]

"It has long been considered that classic motor neuron disease/amyotrophic lateral sclerosis (cMND/ALS) spares cognitive skills. However, there are several historical references to behavioral problem in MND, and descriptive terminology such as schizophrenia and dementia have been used. Motor slowness, lack of control of facial and bulbar emotional expression, and the subsequent effects of depression, sedative drug ingestion, and hypoventilation all contribute to the interpretation of cognitive ability. Nonetheless, neuropsychological examination and functional imaging approaches are showing that a fraction of individuals with cMND/ALS exhibit cognitive impairment that is not explained only by these confounding variables". [4]

"The discovery that a motor neuronopathy develops in a proportion of individuals with established frontotemporal dementia (FTD), which is characterized by degeneration of the frontal and temporal neocortex, is potentially significant in this regard. This FTD/MND syndrome is significant because, due to its slowed progression, it has the potential to shed light on the progression of symptoms in FTD. It refers to the early neuropsychological abnormalities and anatomical changes that occur prior to the spread of disease and secondary degenerative processes that occur in FTD. Furthermore, FTD/MND could influence our knowledge of the cognitive alterations that occur in cMND/ALS". [4]

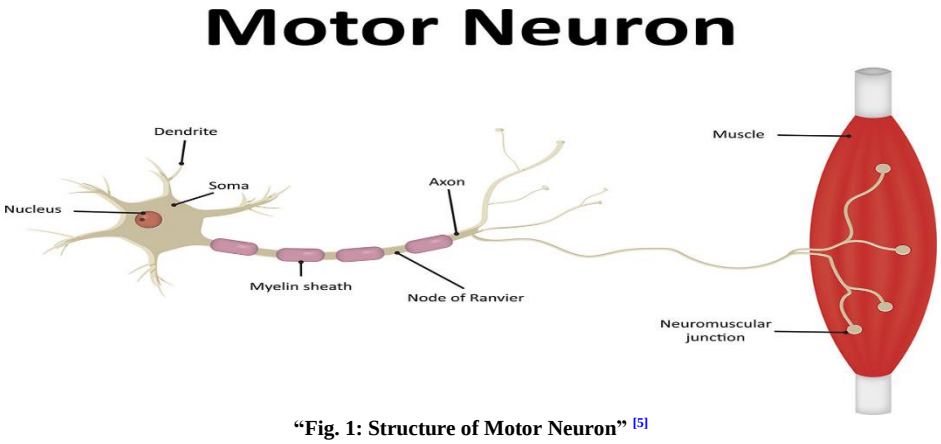
MOTOR NEURON

"Motor neurons (also known as efferent neurons) are nerve cells that transport messages from the central nervous system to muscles in order to induce movement. They produce neurotransmitters that cause muscular action by triggering responses. These motions might be deliberate, like reaching out to pick something up, or involuntary, like moving a hand away from a hot surface". [5]

"Motor neurons are in charge of integrating information from the brain to the muscles, glands, and organs that will perform the necessary motor activity. Because motor neurons allow us to move, talk, eat, swallow, and breathe, we would be unable to perform many basic life activities without them". [5]

Structure of Motor Neuron

"The structure of a motor neuron can be categorized into three components: the soma, the axon, and the dendrites". [5]



"Fig. 1: Structure of Motor Neuron" [5]

- "The nucleus, which controls the cells and produces proteins to keep the neuron working, is located in the soma, which is the cell body.
- The axon is a long extension structure that originates from the soma. The axon's job is to send the information it receives down the neuron's body to the dendrites at the end.
- Dendrites are the branch-like structures that extend from the neuron's ends. These structures help dendrites send and receive information from other neurons". [5]

"Motor neurons are found in the motor cortex, brainstem, and spinal cord of the central nervous system (CNS). Efferent neurons, also known as motor neurons, convey information from the CNS to muscles and other peripheral systems like organs and glands. Afferent neurons, also known as sensory neurons, convey information back to the CNS from sensory organs and tissues". [5]

"The CNS sends information to peripheral organs, muscles, and glands via around 500,000 motor neurons. Efferent fibers are the motor neurons' axons that are responsible for this. The soma of motor neurons is located in the CNS, while the fibers, or axons, project out of the CNS to the location where motor action is intended. The efferent fibers are the longest in the body, with one of the longest axons being able to stretch from the base of the spinal cord to the toes". [5]

Types of Motor Neuron

"Upper motor neurons and lower motor neurons are two types of motor neurons that are distinguished by their function. These neurons control both voluntary and involuntary movements by forming a range of intricate and controlled circuits throughout the body". [5]

1. Upper Motor Neurons

"Upper motor neurons are the major neurons that initiate voluntary movement throughout the body by connecting the cerebral cortex to the brain stem and spinal cord. They can be found in either the motor cortex or the brainstem. Upper motor neurons can travel through a variety of tracts, or pathways, that fulfil diverse functions: pyramid, extrapyramidal, rubrospinal, tectospinal, and reticulospinal tracts.

- Upper motor neurons in the pyramid tract will be in charge of conscious movement. The pyramid tract begins in the frontal lobe's motor strip, and nerve impulses go from there to the spinal cord.
- Any channel outside of the pyramid tract is known as the extrapyramidal tract. These are frequently engaged in motor activities such as posture and balance that are performed subconsciously.
- The rubrospinal tract is an extrapyramidal tract that is responsible for involuntary motions that help the body maintain and enhance its balance.
- Another extrapyramidal tract, the tectospinal tract, controls muscle movement within the neuron.
- The reticulospinal tract is essential for body autonomy". [5]

2. Lower Motor Neurons

"Lower motor neurons, which are found in the spinal cord, are in charge of sending signals to the skeletal muscles, organs, and glands. They take input from the top motor neurons, either directly or through interneurons, and stimulate their activity by extending their fibers all the way to their intended destinations. Lower motor neurons are divided into three types: somatic, specific visceral efferent, and general visceral motor neurons". [5]

a. Somatic motor neurons

"They have axons that extend to skeletal muscles and originate in the central nervous system, specifically the brainstem. Alpha, beta, and gamma motor neurons are subtypes of somatic motor neurons.

i. Alpha motor neurons are massive motor neurons that innervate skeletal muscle and create muscular contractions that allow movement to occur. Extrafusal

muscle fibers, which are ordinary muscle fibers, are specifically innervated.

ii. Beta motor neurons are less well classified than alpha motor neurons, although they are known to innervate both extrafusal muscle fibers and intrafusal fibers, which function as specialized sense organs and are innervated by both motor and sensory fibers.

iii. Stretch receptors in skeletal muscle, commonly known as muscle spindles, activate gamma motor neurons. Despite their name, gamma motor neurons do not directly induce any motor function. Instead, they're assumed to work in tandem with the alphas to fine-tune muscle contraction". [5]

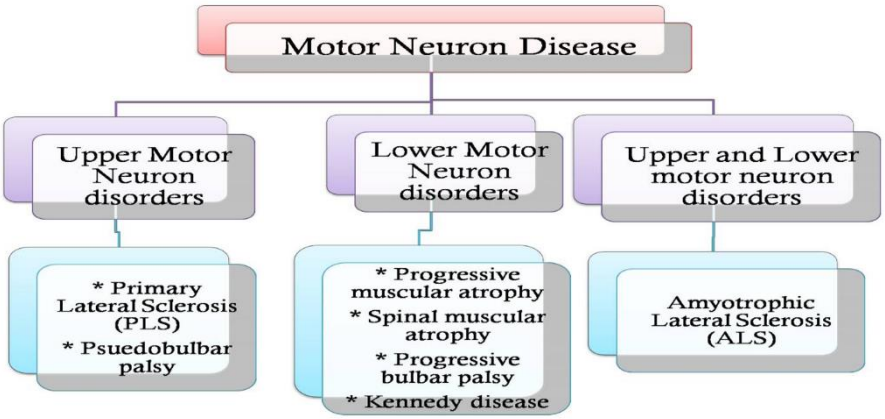
b. Special Visceral Efferent Neurons

"The muscles of the head and neck are innervated by special visceral efferent neurons (also known as branchial motor neurons). These are found in the brain stem and, along with sensory neurons, make up the nuclei of various cranial nerves (trigeminal, facial, glossopharyngeal, vagus, and accessory nerves)". [5]

c. General Visceral Motor Neurons

"Both sympathetic and parasympathetic activities of the autonomic nervous system are aided by general visceral motor neurons (ANS). All peripheral processes, such as innervating the heart, smooth muscle, and glands, are stimulated by the visceral motor neurons, which are not consciously controlled. The skeletal muscles are the only part of the body that is not stimulated". [5]

TYPES OF MOTOR NEURON DISEASES



"Fig. 2: Types of Motor Neuron Diseases" [7]

1. Amyotrophic Lateral Sclerosis (ALS)

"Both your upper and lower motor neurons are affected by ALS. You lose control of the muscles that help you move, talk, chew, swallow, and breathe when you develop ALS. They deteriorate and waste away with time. Muscle stiffness and twitching are other possible symptoms. The majority of the time, ALS is referred to as "sporadic" by doctors. This implies that anyone can obtain it. In the United States, only approximately 5% to 10% of cases are passed down through families. Between the ages of 40 and 60, ALS commonly begins. The majority of persons with the disease live for 3 to 5 years after their symptoms appear, although others can live for up to 10 years". [6]

2. Primary Lateral Sclerosis (PLS)

"PLS resembles ALS in that it affects just the top motor neurons. It causes arm and leg weakness and stiffness, delayed walking, and impaired coordination and balance. Speech becomes garbled and slow. It usually begins in adults between the ages of 40 and 60, just like ALS. Over time, the muscles get stiffer and weaker. People do not die from it, unlike ALS." [6]

3. Progressive Bulbar Palsy (PBP)

"This is a form of ALS. Many persons with this illness will get ALS in the future. PBP causes motor neuron damage in the brain stem, which is located towards the base of the brain. Motor neurons in the stem help you chew, swallow, and speak. You may slur your speech and have difficulty eating and swallowing if you have PBP. It also makes controlling emotions difficult. You may laugh or cry unintentionally". [6]

4. Pseudobulbar Palsy

"Progressive bulbar palsy is similar to this. It affects the motor neurons that control speech, chewing, and swallowing. Pseudobulbar palsy produces uncontrollable laughter or crying". [6] "This form affects about 2 out of every 10 patients with MND". [8]

5. Progressive Muscular Atrophy

"This type is significantly rarer than ALS or PBP. It might be sporadic or inherited. Lower motor neurons are primarily affected by progressive muscular atrophy. Weakness commonly begins in the hands and subsequently spreads across the body. Your muscles may get weak and spasm. This condition has the potential to progress to ALS". [6]

6. Spinal Muscular Atrophy

"Lower motor neurons are affected by this hereditary disease. Spinal muscular atrophy is caused by a mutation in the SMN1 gene. A protein produced by this gene protects your motor neurons. They will perish without it. The upper legs and arms, as well as the trunk, become feeble as a result. SMA is classified into several categories based on when symptoms initially appear:

Type 1 (also known as Werdnig-Hoffmann illness): Begins at the age of six months. This type of child is incapable of sitting or holding their head erect. They have low muscular tone, sluggish reflexes, and difficulty swallowing and breathing.

Type 2: It begins between the ages of 6 and 12. This type of child can sit but not stand or walk on their own. They may also have breathing problems.

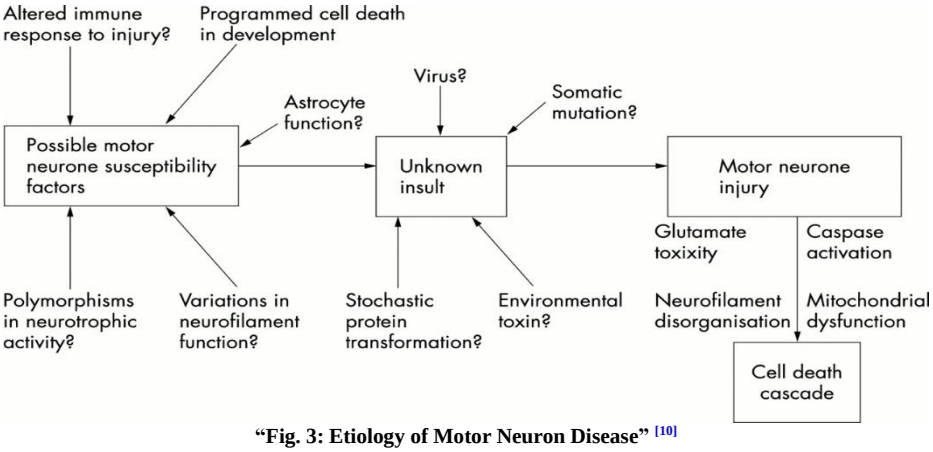
Type 3 (also known as Kugelberg-Welander illness): This is the most severe form of the disease. It begins between the ages of 2 and 17. It has an impact on a child's ability to walk, run, stand up, and climb stairs. This type of child may have a bent spine as well as shortened muscles or tendons surrounding their joints.

Type 4: It usually begins after the age of 30. Muscle weakness, shaking, twitching, and breathing issues are all symptoms of this type. It primarily affects upper arm and leg muscles." [6]

7. Kennedy's Disease

"It's also inherited, and only males are affected. Females can be carriers but are not affected. A woman who carries the Kennedy disease gene has a 50% probability of passing it on to her kid. Shaking hands, muscle cramps and twitches, and weakness in the face, arms, and legs are all symptoms of Kennedy's illness in men. They may have difficulty swallowing and communicating. Men with big breasts and poor sperm counts are common". [6]

ETIOLOGY/CAUSES OF MND



"Fig. 3: Etiology of Motor Neuron Disease" [10]

"The origins of MND are unknown in the majority of patients, and there are presently no medications that effectively protect motor neurons from harm. The search for effective disease-modifying medicines would be considerably aided if the underlying patho-etiology could be better understood. A complex relationship between fixed genetic components and modifiable external stimuli, similar to other neurodegenerative disorders, appears to be the most likely explanation". [9]

1. Genetic Factors

"In 5-10 % of MND patients identified with familial disease, a strong genetic aetiology can be found. Mutations in the copper/zinc superoxide dismutase (SOD1) gene, which codes for an antioxidant defence protein, have been discovered in about 20% of these cases, with over 100 distinct mutations in this gene already described. In adult and juvenile onset familial MND pedigrees, seven more genetic loci have been identified. Five of these genotypes are inherited as an autosomal dominant trait, whereas the other two are recessive. However, only a few of the causal genes (such as alsin, senataxin, and vesicle-associated membrane protein B) have been found, pedigree sizes are tiny, and the disease phenotype is frequently unusual." [9]

"In sporadic cases, both novel and existing mutations in the SOD1 gene have been discovered, however at a significantly lower incidence than in familial disease. Following candidate association studies, several susceptibility genes have been suggested, including the angiogenin, survival motor neuron, and haemochromatosis genes, which may predispose to motor neuron damage, though attempts to reproduce such findings have been inconsistent." [9]

2. Exogenous Factors

"The discovery of unusual geographical and occupational clusters of MND has prompted researchers to look for possibly modifiable environmental and lifestyle factors that could act as disease triggers or modifiers in intrinsically susceptible people. Physical activity, occupation, mechanical and electrical harm, military service, and toxin exposure, particularly heavy metals and pesticides, have all been considered previously. Smoking is the only other likely risk factor identified to yet, aside from the established risks linked with male gender, family history, and increasing age, but this remains contentious." [9]

2.1 Physical activity as an exogenous risk factor in motor neuron disease (MND)

"In the etiology of MND, many potential external risk factors have been hypothesized as part of a gene-environment interaction. Following reports of a greater than predicted incidence of MND in professional athletes, there has been an increasing interest in the role of intensive physical exercise in the development of the disease. Current hypotheses about the cellular and genetic causes of MND also support this conclusion." [9]

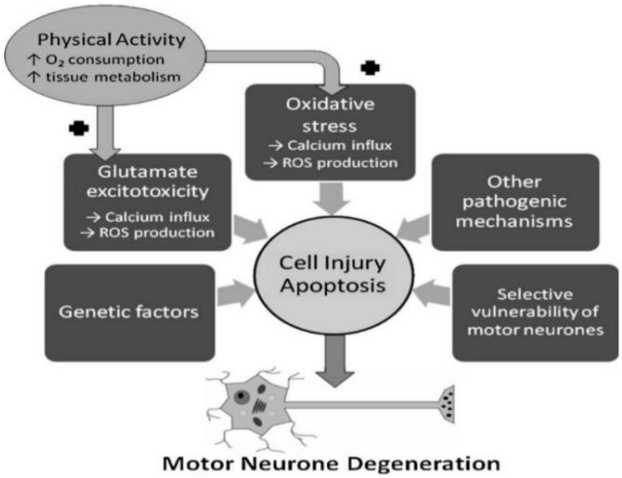
2.1.1 Biological plausibility for Physical Activity (PA) as a risk factor for MND

"Understanding the pathophysiological pathways behind MND has progressed significantly. Unrelated study has also shown that PA alters some of these systems, suggesting a biological explanation for the relationship between MND and PA." [9]

Oxidative Stress

"Oxidative stress is a disease that results from an imbalance in normal metabolism. Excessive free radical generation and/or lack of preventive detoxifying or repair systems cause negative effects of reactive oxygen species (ROS). Both post mortem and in vivo studies have shown abnormally high levels of oxidative damage indicators inside nervous system tissues in MND. A growing body of evidence clearly suggests that oxidative stress is a substantial contributory factor to motor neuron destruction in MND, as seen by SOD1 enzyme failure in familial MND.

Although there is considerable disagreement over whether or not PA causes oxidative stress, it is possible that the increased oxygen intake and tissue metabolism required for strenuous exercise might increase ROS production. Evidence for this was originally reported in 1982, when an increase in free radical concentration in muscle and liver was revealed, and has continued to expand since then. Many theories have been advanced to explain this rise, including changes in mitochondrial activity and the activation of an inflammatory response. [9] This theory is further supported by a systematic compensatory increase in antioxidant capacity following exercise, which includes increased antioxidant enzyme activity and alterations in tissue redox status. The evidence supporting exercise-induced oxidative stress response modulation has now been reviewed multiple times. However, the normal adaptation processes seen in regular moderate exercise may not be achieved during strong PA, resulting in ROS toxicity. These effects may be amplified in people who are unable to mount the regular physiological responses to exercise due to a genetic predisposition." [9]



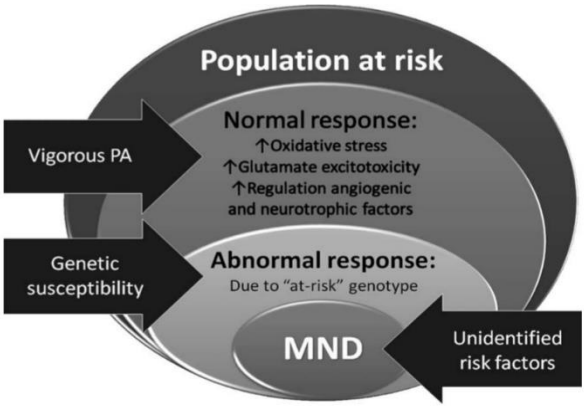
"Fig. 4: Alteration of oxidative stress & glutamate excitotoxicity by Physical Activity" [9]

Glutamate excitotoxicity

"Despite being a key excitatory neurotransmitter, glutamate in higher-than-physiologically-normal concentrations can overstimulate receptors, resulting in excessive calcium ion influx into brain cells and, eventually, neuronal cell death, a process known as glutamate excitotoxicity. According to Beretta et al., concurrent factors such as high levels of PA, nutritional supplements, prescription and illicit medicines, exercise-induced tissue ischemia, and sports-related injuries may exacerbate oxidative stress in soccer players. They speculated that neuroinflammation, another putative pathogenic mechanism in MND, could play a role in the MND-football link, albeit primarily through chronic anti-inflammatory drug usage. Another editorial proposed that "chronic exhaustion of the body's antioxidant capacity" could be a relationship between PA, athletics, and neurotrauma as MND risk factors." [9]

2.1.2 Genetic plausibility for PA as a risk factor for MND

"Several genes linked to the development of MND are now known to be elevated or have their expression altered by PA, suggesting a genetic relationship between the two diseases. The strongest evidence comes from genes with angiogenic and neurotrophic characteristics. However, no research has been published to date that precisely explores gene-environment interactions that may relate PA to MND." [9]



"Fig. 5: Summary of the proposed mechanisms by which physical activity may act as a risk factor for motor neuron disease" [9]

Hypoxia-response genes

"Mutations in hypoxia-induced genes have led to speculation about the role of hypoperfusion in MND development. If the typical response to hypoxia is not possible, the high oxygen requirements of motor neurons may increase their susceptibility to degeneration before other tissues. In support of this, a chance finding in 2001 found that in mice, deletion of the hypoxia response element in the promoter region of the vascular endothelial growth factor (VEGF) gene promotes the development of a phenotypically and pathologically similar disease to MND. Human MND patients have shown variations in the VEGF gene, reduced circulating serum VEGF, and changed VEGF protein and receptor gene transcription." [9]

Neurotrophic factors

"Neurotrophic factors have been shown to protect motor neurons in culture and animal models, leading to clinical trials for insulin-like growth factor-1, ciliary neurotrophic factor (CNTF), glial-derived neurotrophic factor (GDNF), and brain-derived neurotrophic factor (BDNF), despite no significant clinical benefits. Genetic polymorphisms in the genes encoding these neurotrophic factors have also been shown to have pathogenic features. In the context of a SOD1 mutation, a null mutation in the CNTF gene has been linked to early-onset disease in familial MND and mice models, as well as sporadic MND, albeit its prevalence in controls supports a modifying rather than causal involvement. In MND spinal cord autopsy specimens, high serum levels and overexpression of CNTF have also been reported. Two hundred and three genes were elevated and 241 genes were downregulated, including CNTF and leukemia inhibitory factor receptor (LIFr) by at least twofold. Exercise up-regulated 194 genes in muscle, including VEGF receptor 2, and down-regulated 176 genes." [9]

SIGNS AND SYMPTOMS OF MND

"The type of disease determines the initial symptoms. However, weakness in the arms and legs is the most typical early symptom. This is often more noticeable on one side of the body than the other." [12]

Other early symptoms of the disease include:

- "You may trip or find it difficult to climb stairs if you have a weakness in your ankle or leg
- Impaired speech, which might lead to problems eating certain meals
- A weak grip - you may drop things or struggle to open jars or button up buttons.
- Muscular twitches and cramps
- Weight loss - over time, your arm or leg muscles may have thinned.
- Difficulty in stopping yourself from crying or laughing in inappropriate situations" [11]
- "An increasingly stiff, clumsy walk
- General fatigue" [12]

"Motor neuron illness affects either the upper motor neurons in the brain (which cause muscle spasms and excessive reflexes) or the lower motor neurons in the brain stem and spinal cord (causing a gradual wasting and weakness of muscles required for speech, chewing and swallowing). Both the top and lower motor neurons will eventually be impacted." [12]

As the disease worsens, people with motor neuron disease may be unable to:

- Walk
- Use their hands and arms
- Speak clearly, or at all
- Swallow
- Hold up their head.

"Breathing and coughing become harder due to respiratory muscular weakness. Food or saliva aspirated into the lungs is more likely when swallowing is difficult. This raises the chance of a lung infection, which is a common cause of mortality in persons with motor neuron disease." [12]

"There may be some discomfort. The most prevalent causes of pain include musculoskeletal pain, pressure associated with immobility, and muscle cramping. Touch, sight, smell, hearing, and intellect are all unaffected by motor neuron disease. In most cases, the muscles that move the eyes are unaffected. Frontotemporal dementia, a kind of dementia that affects personality and conduct, is sometimes linked to motor neuron disease." [12]

COGNITIVE CHANGE IN MOTOR NEURON DISEASE

Brain-behavior relationships in FTD and FTD/MND

"The dementia patterns in FTD and FTD/MND are nearly identical. FTD/MND, on the other hand, conducts a more localized experiment on the brain, which can be attributed to its slower progression: patients with FTD/MND develop bulbar palsy and typically die within three years from respiratory failure, whereas patients with FTD may live for ten or even fifteen years. The sites of early alteration in FTD and the key structures implicated may be revealed by the untimely death of patients with FTD/MND." [13]

"The most prominent feature of FTD is behavioral alteration. The distribution of disease within the frontal and temporal lobes corresponds to three primary behavioral sub-types." [13] "One subtype is associated with disease in the orbitofrontal lobes and anterior temporal neocortex and is characterized by purposeless overactivity, disinhibition, and distractibility (disinhibited-type). Apathy, inertia, and loss of volition characterize a second subtype, which is associated with more widespread frontal lobe dysfunction spreading into the frontal lobes' dorsolateral convexities (apathetic type). A third, less common subtype is marked by stereotyped, ritualistic behavior and routine conformance, and is linked to disease in the striatum and temporal neocortex (stereotypic-type)." [14]

"Patients with FTD who are apathetic perform the worst on typical frontal executive function tests, and their responses are frequently concrete and perseverative. Although abnormalities can typically be induced on selective attention tests, performance in disinhibited-type patients may be rather normal, providing support for the importance of the orbitomedial frontal lobes in this element of voluntary attention." [15] "The hyperactive, disinhibited sub-type of FTD/MND is generally associated with pathological alterations restricted to the orbitofrontal and temporal neocortex. Subcortical regions, such as the hippocampus and amygdala, are relatively spared. End-stage FTD, on the other hand, can cause pathological changes in the dorsolateral convexities, as well as subcortical regions, the amygdala, and the hippocampus. The orbitofrontal and anterior temporal neocortex are thought to be the first sites of pathological alteration in FTD, with subsequent extension to other areas of the frontal lobe and subcortical tissues." [4]

Cognitive change in cMND/ALS

"Because of pseudobulbar and bulbar palsy, patients with cMND/ALS have difficulties communicating their ideas and feelings and controlling the emotional components of their behavior, making behavioral analysis more difficult. Families do, however, frequently comment on the patient's personality changes. Occupational and physical therapists may notice a lack of initiative and compliance in patients with cMND/ALS, distinguishing them from patients with other peripheral neurological and debilitating illnesses. These characteristics suggest that cMND/ALS patients may experience cognitive changes, notably in the area of executive skills." [4]

"A number of studies have found that people with cMND/ALS experience cognitive problems. These are most typically observed in the field of executive function, according to historical reports. The Wisconsin Card Sorting Test, Picture Sequencing, and Verbal Fluency have all revealed deficiencies. However, impairment on these tests is not always present. Furthermore, whereas some studies have found a generalized, albeit minor, intellectual impairment in people with CMND/ALS, others have found no such impairment. While some studies have found memory impairment in cMND/ALS, others have found memory sparing." [4]

"Differences in study findings are likely due to a range of reasons. Depression, medication, and subclinical hypoventilation all have the potential to impair cognitive performance in people with cMND/ALS, leading to a misattribution of cognitive alterations to the core disease process. Motor sluggishness may contribute to poor performance on timed tests like Verbal fluency, leading to an overestimation of cognitive impairment. Even when compounding variables are taken into consideration, however, these factors do not give a satisfactory explanation, as discrepancies persist. Verbal fluency, for example, has been shown to be impaired even when motor speed is controlled. Furthermore, executive impairment has been found in cMND/ALS patients on non-timed activities such as the Wisconsin Card Sorting Test and Picture Sequencing Task, a test that has previously been proven to be associated with the disease." [4]

Memory in cMND/ALS

"On free recall tasks, memory problems in CMND/ALS have been proven most consistently. Some ascribe this to retrieval failure and inadequate learning techniques as a result of frontal brain damage. On the basis of the larger attentional demands of the visual task, impairments on a visual but not a verbal recognition task have also been interpreted as frontal lobe dysfunction." [16]

"This frontal lobe view would be supported by evidence of abnormalities in selective attention but not memory function in CMND/ALS." [16] "Furthermore, a study using event-related brain potentials revealed that recognition memory deficiencies were caused by poor encoding rather than poor retention over time, which is consistent with a frontal lobe interpretation." [17]

"The findings show no evidence of faster forgetting in patients than in controls, but they do point to a problem with initial information assimilation. These memory results, along with those from previous investigations, are consistent with an interpretation based on poor encoding mechanisms as a result of frontal lobe dysfunction. The discovery of poorer learning of a word list with maintained retention across a delay adds to these findings. That is, knowledge is poorly digested but can be remembered normally once learned. These findings, once again, point to a frontal lobe explanation for memory loss in cMND/ALS." [19]

"It appears that frontal lobe impairment plays a role in patients' memory problems. Whether it provides a sufficient account, or whether changes in hippocampus also have a role remains to be determined." [20]

Language in MND/ALS

"Several studies have shown that cMND/ALS patients perform poorly on language tests. Impairment in word creation, as judged by verbal fluency assessments, is the most commonly reported abnormality, but abnormalities in other domains, such as sentence comprehension and verb processing, may also be present. Language characteristics, interestingly, mostly point to frontal lobe impairment. There is evidence that the frontal lobes play a key role in verb interpretation, which may be reduced differently in frontotemporal dementia." [21]

"The degradation of active propositional speech linked with frontal lobe damage and typical of frontotemporal dementia is described as "reduced verbal fluency and a dependence on stereotyped utterances." [22]

"The extent to which language problems in CMND/ALS constitute real aphasia is a point of contention. A fast-developing aphasic syndrome in patients with MND/ALS has been reported in the literature." [23][24][25] "Progressive aphasia is one of the clinical signs of frontotemporal lobar degeneration, which shares the same pathophysiology as FTD, hence its development in MND/ALS would not be surprising. However, given the rarity of progressive aphasia in comparison to FTD, frank aphasia in conjunction with MND is expected to be uncommon." [4]

"It might be difficult to tell the difference between motor articulatory and language abnormalities, which can make interpreting aphasic symptoms more difficult. Furthermore, language abnormalities can occur for a variety of reasons other than basic aphasia. Higher order executive deficiencies, rather than core linguistic abilities, have been found to induce poor verbal fluency." [26] "Executive impairments, not aphasia, have been blamed for errors in sentence comprehension identified in some individuals who showed no indications of expressive or receptive language impairment." [27] "Lower results on sentence comprehension tasks, on the other hand, have been mentioned in other research as evidence of aphasia. Differences in data interpretation and definitions of aphasia are likely to result in substantially disparate estimations of the prevalence of aphasic symptomatology in cMND/ALS." [24]

The relationship between CMND/ALS and FTD

"In cMND/ALS, functional imaging with SPECT revealed anomalies in the frontal and anterior temporal cortices, which mirrored the pattern of abnormality seen in FTD and FTD/MND, albeit to a lesser extent." [27] "Furthermore, imaging abnormalities in the frontal lobe can be identified in some patients who do not have cognitive problems. The orbital frontal cortex has been proposed as an early location of pathological alteration in FTD. Despite their severe behavioral disturbances, patients with the disinhibited, orbitotemporal variant of FTD may perform neuropsychological tests of executive function rather normally." [4]

"This aspect is consistent with the observation that damage to the orbital regions of the frontal lobe can lead to sociopathic behavior even if there is no evidence of cognitive impairment on standard testing. It's probable that some people with cMND/ALS have pre-clinical FTD/ MND, with the early emotional and behavioral alterations being masked by and difficult to distinguish from the physical manifestations of the disease. It's possible that the distribution and advancement of pathogenic alteration in other cMND/ALS patients is sufficient to cause executive function abnormalities. PET investigations have revealed a relationship between verbal fluency deficiencies and dorsolateral prefrontal brain dysfunction, which supports this theory. To put it another way, overt cognitive impairment is linked to pathological changes in the prefrontal cortex that extend beyond the orbital regions." [28]

"The majority of cMND/ALS research is necessarily cross-sectional. It's important to remember that the distinctions between

FTD/MND and CMND/ALS could be due to the temporal course of the underlying pathogenic alterations in the frontotemporal neocortex and motor neuronal pathways. Many people with cMND/ALS may never acquire FTD in either its behavioral or cognitive aspects due to the disease's short duration. Future molecular biological research will most likely offer insight on the time sequence of cortical versus motor neuron degeneration." [4]

CONCLUSION

Although our understanding of MND pathophysiology has evolved significantly in recent years, the health benefits to patients have been minimal. The task of determining the causes of this deadly disease remains unsolved. Current epidemiology and fundamental scientific research, as well as speculations about the origin of other neurodegenerative illnesses, suggest a complex multiple etiology. With this in mind, researchers are continuing their hunt for endogenous and modifiable exogenous pathogenic possibilities. The current data regarding PA as a risk factor in MND is sparse, contradictory, and of insufficient quality to draw firm conclusions. Many of the issues that have arisen are due to the type and low prevalence of MND. However, the previously observed positive link between MND and PA has not been shown beyond a reasonable doubt, and it could indicate an aberrant physiological reaction to an exogenous stimulus in genetically sensitive individuals.

Despite the fact that there is now a better knowledge of the psychological requirements of MND patients and their families, having a psychologist or psychiatrist as part of the multidisciplinary team is not usual. There are certain holes in the current system. Both in practice and in the standards that guide it. There is a need for a more holistic approach to the care of these patients and their families, based on this review, which identifies a variety of psychological difficulties that effect persons living and dying with MND.

Conflict of Interest: None

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