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Editorial

Dilemma of Motor Neuron Diseases

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Background

Motor neuron diseases (MND) first described by Jean-Martin Charcot 1869, Paris.it is rare disease in the UK about 1 per 50,000 populations every year. MNDS contain several varieties that affect upper or lower motor neurons and may be both. MND affect muscle activities all over the body due to disrupt the signals between nerves & muscles or between upper motor neuron and lower motor neuron. Risk factors include inheritance, around age of 40 years, male much more than female below 65 years as 3:2. The cause of MND still unknown especially inherited one but sporadic may related to viral, toxins like formaldehyde and pesticides, smoking, head trauma, fatty meals or others.

The causes of MNDS still unknown but researches identified many factors intracellular related to MNDS : excess glutamate , accumulation of abnormal proteins ,deficiency of anti-oxidant and neurotrophic factors ,abnormal mitochondria and transportation system , excess prion in ALS cases.

Pathophysiology of ALS simplified as followed stages: Excitotoxicity → elevated intracellular Calcium → mitochondrial overloading by calcium → generation of free oxygen radicle → cell apoptosis (current medical chemistry 17, 2010, 1942-1952).

Pathology of MNDS

Boninan's bodies which intracellular eosinophilic dense granules, Hirano"s bodies (rod shaped contain parallel element, Lewy bodies, Neuritic plaques, Neurofibrillary tangles, decrease nucleolus staining (reduced mRNA, Rrna), loss of glial glutamate transport, loss of muscarinic cholinergic receptors of Anterior Horn cells, decrease acetyltransferase in spinal cord, decreased Glycine and elevated IgG in spinal cord and ghost cells.

Classification of MNDS

MND classified to inherited and sporadic disease. Inherited MND may be autosomal dominant (50% chance of inherited to children), autosomal recessive or x linked (manifested in males & carried by female). There are four categories of MND.

Type	UMN degeneration	LMN degeneration
Amyotrophic lateral sclerosis (ALS)	Yes	Yes
Primary lateral sclerosis (PLS)	Yes	No
Progressive muscular atrophy (PMA)	No	Yes
Progressive bulbar palsy (PBP)	No	Yes
Pseudobulbar palsy	Yes, bulbar muscles	No

Symptoms of MND

Amyotrophic lateral scleroses (ALS) affect both upper and lower motor neurons, usually fatal. it begins by weakness in arm, leg or swallowing disorder (bulbar) bilaterally till affect muscles of respiration (diapgram and intercostal muscles) lead to arrest respiration if the patient did not ventilate mechanically. ALS usually did not affect higher cognitive functions except in few cases. Death in these patients usually due to arrest of respiration in less than five years. Genetic predisposing in familial form less than 10% of the cases due to mutations of the superoxide dismutase gene, or SOD1, present in chromosome 21.

Primary lateral sclerosis (PLS) affect upper motor neurons in cerebral cortex controlling limbs and face slowing the movement and increasing its difficulty, its course begins from lower limb upwards till affect bulbar muscles. PLS affect men than woman, gradual progressive course with subsequent clumsy hands and stiffness of both lower limbs.

Progressive bulbar palsy (PBP) involving brainstem and lower motor neurons which control swallowing, speech, so symptoms begin by swallowing disorder, speech difficulties and tongue atrophy with fasciculation then progressive weakness in four limbs but less evident than the bulbar palsy with subsequent aspiration pneumonia. Some patients suffering from emotion liability.

Pseudo bulbar palsy (PSBP) affects upper motor neurons which disrupt lower motor neurons n brainstem. These patients suffering from expressionless faces, chocking and other symptoms of bulbar palsy with difficulty to protrude tongue, others may have also emotion liability.

Progressive muscular atrophy (PMA) affect lower motor neurons with slower onset but continuous progressive course beginning from the hands downwards manifested as clumsy hands. PMA may progress to ALS.

Post-polio syndrome (PPS) which affect group of muscles previously its nerves suffered poliomyelitis few decades before due to illness, trauma or degeneration .PPS may be mild or sever according to the severity of polio before. PPS is not fetal.

Diagnosis of MNDS

MNDS can mimic other diseases especially in early case, so complete physical and neurological examination is mandatory including higher cognitive function, behavior, motor, sensory, speech, visual, hearing, coordinator and fine skills. No specific tool can diagnose MNDS but EMG (Electromyography) can detect lower motor neuron disease, muscle dysfunction and peripheral nerves lesions through abnormal electrical waves (low or higher amplitude, positive waves and fibrillation potentials). Nerve Conduction Velocity (NCV) usually done to assess peripheral and sensory nerves.

Laboratory tests such CSF (Cerebrospinal fluid) to rule out inflammatory cause, high protein creative kinase in muscle disease Radiology like MRI (magnetic resonant imaging) to detect brain and spinal cord tumours, trauma, inflammatory lesions or other diseases like MS (multiple sclerosis). MRIS (spectroscopy) can help in diagnosis of upper motor neuron disease.

Biopsy of nerves and muscles via small incision or needle followed by microscopic examination proofing the diagnosis in some cases.

Lastly through Tran's cranial magnetic stimulation with recording electrical evoked potential diagnose MNDS and upper motor neuron lesion.

Treatment of MNDS

No cure for this disease most of drugs are symptomatic. Riluzole is the only drug which FDA approved for ALS treatment by decrease production of glutamate that destroy motor neurons, prolong survival for less than 3 months Riluzole may be used with Tamoxifen. Arimoclomol as co-inducer of heat shock protein. Antisense Oligonucleotide reduce SOD1 and m RNA levels with slowing the course of MNDS especially earl other symptomatic treatment includes non-steroidal anti-inflammatory or anticonvulsant to reduce pain, antidepressant, muscle relaxant like baclofen & benzo diazepam, botulinum toxin to relief spasticity, dextromethorphan and quinidine to diminish pseudobulbar palsy, opiates in terminal cases to relief their pain.

Rehabilitation and physical therapy can improve stature, enhance muscle power and reduce spasticity, improve swallowing disorders, speech …etc.

Good Nutrition is mandatory for these patients but in ALS patients may in need for gastrostomy. some patient due to weakness in respiratory muscles need mechanical ventilation. One study revealed eating foods high in omega-3 unsaturated fatty acids may decrease the risk of developing ALS.

Prognosis

According to type of MNDS in ALS it is fetal with few months but in PLS may progress more slowly with longer survival.

Coming Soon

All of new researches focusing on understanding the developing of MNDS for better management; it includes drugs, stem cells and genetic engineering. Example of the drugs ceftriaxone (antibiotic) can improve nerve cells protection via decrease glutamate and this study in multicenter early clinical study.

Other study through usage of stem cells implantation in brain and spinal cord or intrathecal injection to promote protection by decrease production of toxic SOD1 protein in ALS while administration of dexpramipexole enhance protection by maintain integrity of mitochondria that enhance integrity of nerve cells. Promising drugs like lithium, minocycline and co enzyme Q10 play role in future management. Researchers in Stanford University School of Medicine published in Nature Genetics (October 2012) that by using baker's yeast, they discovered a "chink in the armor" of ALS . This will open new possibilities for new line of MNDS treatment.

Bibliography

1. Andersen PM. "Amyotrophic lateral sclerosis associated with mutations in the CuZn superoxide dismutase gene". *Current Neurology and Neuroscience Report* 6.1 (2006): 37-46.
2. Boillee S ., *et al.* "ALS: a disease of motor neurons and their nonneuronal neighbours". *Neuron* 52.1 (2006): 39-59.
3. Bruijn L and Cudkowicz M. "Therapeutic targets for amyotrophic lateral sclerosis: current treatments and prospects for more effective therapies expert rev". *Neorotherapeutics* 6.3 (2006): 417-428.
4. Cronin S., *et al*. "Ethnic variation in the incidence of ALS; a systemic review". *Neurology* 68.13 (2007): 1002.
5. Cudkowicz M., *et al*. "A multicenter, dose ranking safety and pharmacokinetic study of arimoclomol in ALS". *Amyotrophic Lateral Sclerosis* 7.S1 (2006): 113.
6. Kim S., *et al*. "Effectiveness of recombinant human erythropoietin therapy in amyotrophic lateral sclerosis". *Journal of Clinical Neurology* 10.4 (2006): 342-347.
7. Kurland LT and Mulder DW. "Epidemiologic investigations of amyotrophic lateral sclerosis. I. Preliminary report on geographic distribution, with special reference to the Mariana Islands, including clinical and pathologic observations". *Neurology* 4.5 (1954): 355-378.
8. Li M., *et al*. "Functional role of caspase 1 and 3 in ALS". *Science* 288.5464 (2000): 335-339.
9. Manfredi G., *et al*. "Mitochondrial dysfunction and energy metabolism in amyotrophic lateral sclerosis". *Biochemical Biophysics Acta* 1802.1 (2006): 323-331.
10. Moisse K and Strong M. "Innate immunity in amyotrophic lateral sclerosis". *Biochimica et Biophysica Acta* 42.3 (2006): 1083-1093.
11. Rothstein JD., *et al*. "β-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression". *Nature* 433.7021 (2005) : 73-77.
12. Rowland Lp and Schneider N. "Amyotrophic lateral sclerosis". *New England Journal of Medicine* 344.22 (2002): 1691-1700.
13. Sarkar S., *et al*. "Lithium induces autophagy by inhibiting inositol monophosphatase". *The Journal of Cell Biology* 170.7 (2005): 1101-1111.
14. Smith RA., *et al*. "Antisense oligonucleotide therapy for neurodegenerative disease". *Journal of Clinical Investigation* 116.8 (2006): 290-297.

15. Traynor BJ., *et al*. "Neuroprotective agents for clinical trials in ALS: a systematic assessment". *Neurology* 67.1 (2006): 20-27.
16. Van Den Bosch L., *et al*. "The role of excitotoxicity in the pathogenesis of amyotrophic lateral sclerosis". *Biochimica et Biophysica Acta* 1762.11-12 (2006): 1068-1082.
17. Veldink JH., *et al*. "Physical activity and the association with sporadic ALS". *Neurology* 64.2 (2005): 241-245.
18. Wang J., *et al*. "Coincident thresholds of mutant protein for paralytic disease and protein aggregation caused by restrictively expressed superoxide dismutase cDNA". *Neurobiology Disease* 20.3 (2005): 943-952.
19. Worms pm. "The epidemiology of motor neuron disorder;a review of recent studies". *The Journal of Neuroscience* 191.1- (2001): 3-9.
20. Yoshino H and Kimura A. "Investigation of the therapeutic effects of edaravone, a free radical scavenger, on amyotrophic lateral sclerosis". *Amyotrophic Lateral Sclerosis and Frontotemporal* 7.4 (2006): 241-245.

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