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Letter to the Editor

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Perspectives in Motor Neuron Disease and Amyotrophic Lateral Sclerosis

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Abstract

Several genetic markers have been identified as predisposing factors in the aetiology of motor neuron disease, MND /ALS. Chief among these are mutations in the SOD1 gene but many other aberration of the genome have been implicated mainly in the form of structural variants (SVs). Comparison is made between sporadic MND/ALS and a similar degenerative disorder endemic on the island of Guam known to be caused by Cycad toxicity. The long incubation period of both conditions points to a complex time-dependent pathogenesis.

Perspectives

Motor neuron disease (MND) is characterised as a progressive degeneration of the anterior horn cells of the spinal cord (lower motor neurons). When MND is combined with an upper motor neuron component it is known as Amyotrophic Lateral Sclerosis (ALS). MND manifests clinically as a progressive lower motor neuron disorder with muscle weakness and atrophy .When combined with ALS there are additional signs of upper motor neuron involvement such as spasticity and exaggerated tendon reflexes.

The key element of the pathology of MND/ALS is the degeneration of spinal motor neurons (anterior horn cells, AHC) and atrophy with gliosis of the lateral corticospinal tracts. Clinically MND causes progressive muscular atrophy and flaccid weakness beginning distally in the upper and lower limbs. Fasciculations and fibrillations are present in the affected muscles. Less commonly MND commences around the mouth, tongue and throat. This variant of MND is designated as progressive bulbar palsy referring to the degeneration of the lower cranial nerves arising from the medulla oblongata (i.e. The "bulb "of the brain stem).

The hundred, or more, individual muscle fibres innervated by the branching of the axon of each anterior horn cell is designated as the motor unit. As the disease progresses and individual muscle fibres lose their innervation they become re- innervated from surviving neighbouring motor axons. Histologically the number of atrophic muscle fibres of each affected motor unit are collected close together in an arrangement known as "group atrophy". Re-innervated muscle fibres become hypertrophic. Neighbouring atrophic groups have muscle fibres of different diameters indicating progression as each AHC dies off.

Although the molecular aetiology of MND/ALS is not fully understood many genes have been implicated in its pathogenesis. Chief among these is a mutation in the CU/ZN Superoxide Dismutase gene (SOD1) which manifests as a harmful toxic gain of function. Pathogenic mutations of SOD1 account for 15-20% of familial fALS and about 2% of sporadic sALS. Other genes with mutations or structural variants (SVs) associated aetiologically with both hereditary

fALS and sporadic sALS are C9orf72, TARDBP, FUS and TDP43. Missense or other mutations in the genes which underlie MND/ALS cause damage to the nerve cell by oxidative stress and RNA dysregulation. More recently additional abnormalities in the genome have been linked to the disease. The most notable of these are repeat expansions in C9orf72 and a tri-nucleotide repeat in ATXN2 both genes being implicated in sALS and fALS. More than 40 genetic abnormalities are known to be associated with ALS [1, 4]. Experiments in animals designed to supress the mutated SOD 1 gene by the introduction of anti-sense oligonucleotides have been shown to be some value in protecting the nerve cell from degeneration. Human trials are in progress. Another experimental approach in suppressing mutated SOD1 is by the injection of adeno-associated virus micro RNAs [2, 3].

The burning question in ALS research concerns the aetiology and pathogenesis of the disorder. In this respect certain comparisons between ALS /MND and the Guamanian ALS /Parkinson's Disease and Dementia Complex may provide some clues as there are strong parallels between the two conditions in particular their very long incubation periods. Guamanian ALS/PD Dementia complex is known to be caused by the ingestion of an extract of the nut of the Cycad Zamia palm indigenous to the island. The harmful agent of the Cycad is the glycoside cycasin, a neurotoxic agent .The toxic component of cycasin has been identified as methylazoxymethanol (MAM) [5].

In years past the Chamorro natives of Guam were in the habit of drinking a concoction of the Cycad nut of the Zamia palm as a "tea" as it had stimulant qualities. However their means of detoxification by several washes of the essence turned out to be inadequate so that the neurodegenerative disorder developed after many years of 'incubation'. Why the neurodegeneration manifested clinically after a long delay of so many years is a key question.

A similar enigma pertains to classical ALS/ MND in the sense that the underlying genetic factors such as the SOD 1 mutation, are necessarily present from conception onward yet the clinical disease does not develop until adult life, at the age of 50 years or more. This long 'incubation 'period suggests a complex pathogenesis possibly initiated by environmental factors contributing to the neuronal degeneration. Solvents and pesticides have been anecdotally implicated in this regard.

The long incubation period applicable in both conditions suggests a common pathogenic mechanism for the Guamanian ALS /PD Dementia Complex and classical MND/ALS outside of Guam. One such possibility pertaining to both is a disturbance of the microtubular transport system of the motor axon. Trophic factors are delivered to the motor unit by the anterograde micro-tubular system. Stathmin 2, which regulates microtubule stability, is encoded by the STMN2 gene itself regulated by the RNA splicing factor TDP43 [1]. TDP 43 genotype is known to be associated with the earlier development of sporadic ALS .Structural variants consisting of long CA 24 or more repeats have been shown to influence the age of onset of sporadic ALS [1] STMN2 expression is reduced in both familial and sporadic ALS with TDP43 pathology suggesting the possibility of an perturbed microtubular system. These tentative pathogenetic comparisons between Guamanian ALS/PD and classical MND/ALS are worthy of further investigation.

Chief among the experimental treatments for MND/ ALS is the introduction of stem cells designed to replace the lost motor neurons of the spinal cord. Such stem cells would need to differentiate into anterior horn cells and able to grow out axons to re-innervate the atrophic muscle fibres under the control of the upper motor neuron. While waiting for a cure to be found the arrest the progress of the condition in its earliest stages of degeneration would be is a realistic less ambitious approach. It is anticipated that such a desirable outcome will soon become available from the rapidly advancing field of molecular genetic MND /ALS research [4].

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