Karolinska Institutet

Institutet för Miljömedicin

Studies on metals in motor neuron disease

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Bergendorffssalen, Nobels väg 13

Fredagen den 8 mars, klockan 09.30

av

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ABSTRACT

A slow but steady increase in neurodegenerative disorders has been noted in recent decades. Degenerations in the nervous system are found in Alzheimer´s disease, Parkinson´s disease and motor neuron diseases. Amyotrophic lateral sclerosis (ALS) is the most common of the motor neuron diseases. It is often considered a model disorder of neurodegeneration. Early symptoms of ALS are limb weakness or weakness in muscles of speech and swallowing. Muscle atrophy follow and a slowly progressing paralysis spreads to respiratory muscles invariably leading to death in respiratory failure. Neurophysiological investigations are necessary for proper diagnosis, and it is important to rule out treatable diagnostic alternatives such as myopathies or polyneuropathies.

The cause of ALS is unknown. Prevailing theories include genetic, viral, inflammatory, oxidative or toxic mechanisms. Some indications point toward metallotoxic etiologies. Clusters of ALS have been observed in regions where geological conditions cause elevated metal concentrations in water and soil. Several studies show increased frequency of ALS in certain occupations. ALS-like conditions are found in animals, notably in horses, where metal exposure can be suspected. In addition animal metal exposure experiments show accumulations of metals in the spinal cord.

The aim of this thesis project is to clarify the role of metals in ALS. The hypothesis tested is that neurotoxic metals contribute significantly to the pathogenesis of ALS.
To study this we have measured concentrations of 22 metals in cerebrospinal fluid (CSF) and plasma from patients with ALS and from controls, and correlated findings to literature data to suggest a model for ALS pathogenesis.

Increased concentrations were found for the metals manganese, aluminum, cadmium, cobalt, copper, zinc, lead, vanadium and uranium in CSF from patients with ALS compared to controls. Manganese showed the most prominent correlation. Simultaneous sampling from plasma did not show these elevated concentrations, indicating metal accumulations in ALS CSF. Most of the metals detected in CSF from ALS patients are neurotoxicants.

Studies of mercury distribution in a monkey showed mercury accumulations in the spinal cord after respiratory exposure to mercury. Motor neurons of the spinal cord seem to be more vulnerable to metal toxicity then surrounding cells, as they lack protection from the metal-binding protein metallothionein. Patient exposure to metals, distribution by the bloodstream, penetration of protective barriers and direct toxic effects on neurons of the spinal cord is suggested to be causative in ALS.

It is concluded that neurotoxic metals can reach and affect the anterior horn cells of motor neurons and thereby contribute to the pathogenesis of ALS.

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