Motor neuron uptake of low dose inorganic mercury. Pamphlett R Waley P J Neurol Sci (1996 Jan) 135(1):63-7

In animals, inorganic mercury can bypass the blood brain barrier and enter motor neurons. We sought to determine the lowest injected dose of mercury that could be detected in mouse motor neurons. Mice were injected intraperitoneally with mercuric chloride in doses from 0.05 to 2 micrograms/g body weight and studied between 5 days and 18 months after injection. After formalin fixation, 7 microns sections of cerebrum, cerebellum, brain stem, spinal cord and kidney were stained with silver nitrate autometallography. Five days after injection, mercury granules were detected at doses from 0.2 microgram/g upwards in the cell bodies of spinal and brain stem motor neurons, more granules being seen at the higher doses. Mercury granules were also seen in 5% of posterior root ganglion neurons. At doses from 0.05 microgram/g upwards mercury was detected 5 days later in renal tubule cells. Mercury was still present in motor neurons 6-11 months after injection, but by this time mercury had been cleared from the kidneys. Low doses of inorganic mercury are therefore selectively taken up and retained by motor neurons, making this neurotoxin a good candidate for a cause of sporadic motor neuron disease.

Recovery from amyotrophic lateral sclerosis and from allergy after removal of dental amalgam fillings. Redhe O & Pleva J Int J Risk & Safety in Med 4:229-236 (1994)

"...Five months after the completion of DA removal (29 August 1984) the patient was called for a week-long investigation at the same University clinic where the diagnosis ALS had been made. She felt now extraordinarily healthy and her health status was also confirmed by the words in her record: "The neurologic status is completely without comment. Hence, the patient does not show any motor neuron disease of type ALS. She has been informed that she is in neurological respect fully healthy." ...At the time of writing (early 1993), 9 years have elapsed since removal of the DA fillings, and the patient continues to enjoy good health ... "

. Metallothionein in ALS Motor Neurons. Kasarskis, EJ FEDRIP Database, National Technical Information Service (NTIS).

ABSTRACT: Amyotrophic Lateral Sclerosis (ALS) is a chronic neurodegenerative disease, recognized clinically by its relentless progression of muscle atrophy, weakness, and eventual fatal outcome due to respiratory insufficiency. The illness has no effective treatment. The pathological hallmark of ALS is a selective death of motor neurons in the spinal cord and motor cortex. These features of ALS, however, fail to provide insight into its etiology with the result that several theories of etiopathogenesis have been advanced.

Our research focus is upon the potential involvement of toxic trace metals in causing the death of motor neurons. Heretofore, studies of toxic metals have only considered the possibility of excessive accumulation of a metal in the brain and spinal cord. Our work advanced the notion that mercury is present

to excess in ALS patients when compared to age-matched controls based on a multi-element analytical study using neutron activation analysis of several types of tissue. Further studies have suggested that mercury may be localized within spinal motor neurons using photoemulsion histochemistry. Thus, it appears that mercury accumulates within the very cells which degenerate in ALS, suggesting that mercury may be a necessary precondition for ALS-type degeneration to occur.

BIOPROBE VOLUME 9 Issue 5 Sept. 1993
LOU GEHRIG'S DISEASE (ALS) THE MERCURY CONNECTION!

It cannot yet be said that mercury has been absolutely proven to be a causative factor in the development of ALS (Amyotrophic Lateral Sclerosis; " Lou Gehrig's Disease"); but recently published research definitely points to that probability.

As early as the mid 1950's, it had been established that the clinical features of chronic mercury intoxication at times mimic motor neuron disease. Subsequently, a number of case studies of ALS-like neuropathies caused by various forms of mercury have been documented.

Trace Element Imbalances In Amyotrophic Lateral Sclerosis Khare, SS; Ehmann, WD; Kasarskis, EJ; Markesbery, WR. Neurotoxicology. 11: 521-32. 1990.

ABSTRACT: Concentrations of 15 elements were determined by instrumental neutron activation analysis in brain, spinal cord, blood cells, serum and nails of Amyotrophic Lateral Sclerosis (ALS) patients and appropriately matched control subjects. Several significant imbalances were detected in trace element levels in ALS samples compared to control samples. Some of these changes are probably secondary to the loss of tissue mass, especially in spinal cord. However the widespread changes observed in Hg and se levels in ALS tissues deserve special attention. The significance of these alterations in trace element levels in relation to the pathogenesis of ALS is discussed.

The authors stated: "The changes observed in Hg concentration and the interactions of Hg and se are worthy of special comment and may possibly be relevant to the pathogenesis of ALS. Although an exact mechanism of Hg neurotoxicity has not yet been elucidated, Hg is known to have a high affinity for the sulfhydryl groups of proteins and may subsequently inactivate a protein or an enzyme. This could lead to total inhibition of the cellular function and to cell death."

BIO-PROBE COMMENT: The authors also discussed the significance of the selenium depletion, particularly in light of its established importance in the detoxification of mercury and protection against the adverse effects of mercury. This subject is discussed in detail in the following, more recent and

comprehensive publication, which also addressed other important topics such as why ALS may develop in some individuals exposed to harmful agents (such as mercury) but not others.

TRACE METALS IN HUMAN NEURODEGENERATIVE DISEASES
Kasarskis, EJ; Ehmann, WD; Markesberry, WR. Essential and Toxic Trace Elements in Human Health and Disease: An Update. Pg. 299-310. Wiley-Liss, Inc. 1993.

INTRODUCTION

Several examples of trace metal neurotoxicity causing recognizable classic syndromes have now been established. These have been documented resulting from subacute or sustained chronic exposure to a toxic metal from an identified environmental source or by intentional poisoning.

Implicating toxic metals in the aetiology or pathogenesis of chronic neurodegenerative diseases is more challenging for several reasons:

1. Dating the onset of the human neurodegenerative disease is uncertain, thereby making the identification of the source of exposure by epidemiologic study difficult. As a further complication of this factor, a significant degree of neuronal loss must occur before clinical dysfunction is apparent. In the case of ALS, it has been shown that 50% of spinal motor neurons will have degenerated before the typical features of the disease are noticed. Therefore, the exposure to a harmful neurotoxin could have occurred many years preceding the clinical onset of the disease.

2. Neurodegenerative disorders are caused by the death of select neurons, rather than wholesale destruction of tissue. The neurotoxin could therefore be very specific in its action and effective at a low dose, making systemic toxicity less likely.

3. Biopsy material is not usually available until post-mortem, which is at the end-stage of the disease. At this point, trace metal analysis of brain and spinal cord may not accurately reflect the biochemical condition when the disease process was set in motion.

THE PATHOLOGY OF ALS

Amyotrophic Lateral Sclerosis is a chronic neurodegenerative disease. It is characterized clinically by progressive atrophy and weakness of skeletal muscle and small local involuntary muscular contractions visible under the skin. Although clinical variants and familial forms of ALS occur, the classical disease is readily identified by physical findings and electrophysiological studies.

Pathologically, ALS is characterized by atrophy and degeneration of selective motor neurons in the ventral spinal cord and the motor cortex.

The aetiology and pathogenesis of ALS are unknown. Viral inclusions have not been found, but study of the 5-10% of patients with a familial pattern suggest that a genetic defect may render motor neurons more susceptible to other secondary insults, such as exposure to an exogenous toxin.

THE INVOLVEMENT OF TOXIC METALS IN ALS

The toxic trace element theory of the pathogenesis of ALS has received considerable support and derives its attractiveness from three sources:

1. Epidemiologic considerations indicate that long-term exposure to heavy metal is more common among ALS patients compared to controls.
2. An ALS-like syndrome has been linked to chronic intoxication with mercury and lead.
3. Environmental factors have been implicated in the etiology of a related motor neuron disorder, ie, ALS/Parkinson' s/Dementia in Guamanian subjects.

To date, most studies have examined a very basic hypothesis, that ALS may be caused by chronic, low-level exposure to toxic metals. If this hypothesis is true, then one should be able to analyze tissue from ALS patients and demonstrate that the concentration of toxic metals is higher in ALS compared to age-matched controls.

RESULTS

We began our studies of ALS in this traditional mode by analyzing several tissues (brain, spinal cord, serum, blood cells, and nails) from patients and controls for 15 elements by instrumental neutron activation analysis (INAA). The most important finding was a significant elevation of mercury in brain, blood cells, and serum in ALS patients compared to age- matched controls. The elevation of mercury in ALS could reflect a true excess of body burden of mercury, altered turnover, or perhaps binding to unusual intracellular ligands.

The results of our study also indicated that selenium was reduced in the serum and blood cells of ALS patients. The data were more striking when the ratio of mercury:selenium was computed for each sample in order to study both elements concurrently. This approach not only considered the accumulation of a toxic metal, but also evaluated the integrity of potential detoxification mechanisms. The results of our work indicated that mercury was present to excess relative to selenium in ALS blood cells, serum, and brain.

We have considered that mercury accumulation in motor neurons may be a necessary precondition for ALS-type degeneration to occur. This hypothesis predicts that mercury should be enriched in spinal motor neurons of normal spinal cords and that additional factors would impinge on motor neurons to cause their degeneration in ALS. Our formulation is specific in proposing:

1. Mercury accumulation by neurons is a prerequisite for subsequent neurodegenerative changes to ensue.

2. The ALS phenotype develops either by excessive mercury accumulation or inadequate mercury detoxification.

If mercury is, in fact, an etiologic factor in the pathogenesis of ALS, then one would predict the mercury would accumulate in precisely those neurons which ultimately degenerate in ALS. In order to evaluate this hypothesis, the analysis of mercury must be investigated on a cell-by- cell basis.

Because LAMMS (Laser-Activated Microprobe Mass Analysis) did not provide the requisite sensitivity to detect mercury under our conditions, the mercury-specific photoemulsion histochemical (PH) method described by Moller-Madsen and Danscher in 1986 was adapted to human postmortem spinal cord. Mercury was found localized primarily to the nucleus of motor neurons with lesser amounts seen in the cytoplasm. Mercury was also found associated with spinal motor neurons in normal humans. These data, together with the results of the buLk tissue analyses, indicate that spinal motor neurons have an avidity [ED: Strong affinity] for mercury which could possible render them more susceptible to other neurotoxic agents, thereby conferring a selective vulnerability to neuronal degeneration.

METALLOTHIONEIN IN ALS: SOME SPECULATIONS AND DIRECTION FOR FUTURE RESEARCH.

Metal detoxification may be the more critical factor in the pathogenesis of ALS because it appears unlikely that ALS results from a simple, environmental-type exposure based upon population studies.

The metallothionein (MT) family of proteins has not been investigated in ALS. The rationale for studying MT in ALS receives support from the detailed understanding of MT from human and animal studies.

Our preliminary data implies that at least part of the accumulated mercury may be bound to MT in motor neurons. It is premature to seriously speculate on potential mechanisms, although MT could directly detoxify mercury. Alternatively, mercury could conceivably divert MT from its function in copper and zinc homeostasis.

Our findings suggest a potential mechanism to explain the selective death of spinal motor neurons in ALS, namely an imbalance between mercury accumulation and detoxification of mercury. Our hypothesis considers that inadequate mercury detoxification by MT might occur in ALS spinal and cortical motor neurons leading to neuronal death. Impaired detoxification could result from an aberrant MT isoform within spinal motor neurons or altered MT gene expression following mercury exposure.

BIO-PROBE COMMENT: This presentation is dramatic and compelling. The credentials of the investigators, institutions, and publications are impressive. The techniques, investigative protocols and rationale are beyond reproach.

It should be obvious to even the most biased, that continued acceptance of doctrines and rationales that permit human chronic low-level exposure to mercury, are totally without scientific support, and cannot be condoned any longer.

Inorganic mercury is transported from muscular nerve terminals to spinal and brainstem motoneurons. Arvidson B. Muscle Nerve. 15(10):1089-1094, Oct 1992.

ABSTRACT: The distribution of mercury within the brainstem and spinal cord of mice was investigated with the autometallographic technique after intramuscular administration of a single dose of mercuric mercury (HgCl2). Deposits of mercury were localized to motor neurons of the spinal cord and to brainstem motor nuclei; i.e., neurons with their peripheral projections outside the blood-brain barrier. Unilateral ligation of the hypoglossal nerve prior to the injection of HgCl2 prevented the accumulation of mercury deposits in the ipsilateral hypoglossal nucleus. The selective accumulation of mercury in spinal and brainstem motoneurons is most probably due to a leakage of metal-protein complexes from capillaries in muscle into myoneural junctions, followed by uptake into nerve terminals and retrograde axonal transport. The possible link between this process and the development of motor neuron degeneration in ALS is discussed.

BIO-PROBE COMMENT: It is time that the medical profession took cognizance of the fact that some Amyotrophic lateral sclerosis (ALS) patients improve or become symptom free after amalgam replacement. Animal and human research studies are providing the scientific basis and support to ALS patient case histories reflecting amelioration or cure of this "incurable" disease.

Motor Neuron Uptake of Low Dose Inorganic Mercury. Pamphlett, R; Waley, P. J Neurological Sciences, 135:63-7,1996.

ABSTRACT: In animals, inorganic mercury can bypass the blood brain barrier and enter motor neurons. We sought to determine the lowest injected dose of mercury that could be detected in mouse motor neurons. Mice were injected intraperitoneally with mercuric chloride in doses from 0.05 micrograms/g body weight and studied between 5 days and 18 months after injection. After formalin fixation, 7 micrometer sections of cerebrum, cerebellum, brain stem, spinal cord and kidney were stained with silver nitrate autometallography. Five days after injection, mercury granules were detected at doses from 0.2 micrograms/gram upwards in the cell bodies of spinal and brain stem motor neurons, more granules being seen at the higher doses. Mercury granules were also seen in 5 % of posterior root ganglion neurons. At doses from 0.05 micrograms/gram upwards mercury was detected 5 days later in renal tubule cells. Mercury was still present in motor neurons 6-11 months after injection, but by this time mercury had been cleared from kidneys. Low doses of inorganic mercury are therfore selectivel taken up and retained by motor neurons, making this nurotoxin a good candidate for cause of sporadic motor neuron disease.

BIO-PROBE COMMENT: This new study should be of great interest to scientists who have already connected exposure to mercury to motor neuron diseases such as Amyotrophic Lateral Sclerosis (Lou Gehrig's Disease). Previous research, dating back to the 1960's, has demonstrated that inorganic mercury (Hg 2+ does penetrate the blood-brain barrier, but at a low rate. Mercury vapor, the form released from dental amalgam fillings penetrates the blood-brain barrier far more readily. We must also consider that the above findings represent findings from just a single dose, whereas patients with amalgam fillings receive thousands of doses of mercury vapour every day.