NEUROLOGICAL AND BEHAVIORAL TOXICOLOGY OF INCREASED LEAD ABSORPTION

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A B S T R A C T

Neurologic symptoms play a prominent part in acute lead poisoning and growing evidence suggests an etiologic role of chronic increased lead absorption in several chronic neurologic diseases. A type of motor neuron disease characterized by symmetrical distal muscle wasting, slow progression, and a history of extensive exposure to lead was reported. Although response to chelation therapy was inconclusive, a therapeutic trial of chelation in any patient with motor neuron disease and history of major lead exposure was recommended. Delayed nerve conduction was demonstrated in guinea pigs slowly poisoned with lead acetate, and subsequently, electrophysiologic abnormalities were found in asymtomatic lead workers. Because of these and other similar findings, neurologists and behavioralists are questioning the adequacy of present standards of safe lead absorption.

A good way to demonstrate the spectrum of neurologic disease seen with increased lead absorption and to illustrate the problems that neurologists face when dealing with such patients is to present a few clinical case reports.

The first case concerns a man, aged fifty-one years, who worked in a secondary lead smelter for three and one-half years before developing headache, constipation, abdominal pain, metallic taste in his mouth, nausea, vomiting, and bleeding from the gums. He was treated with two five-day courses of Calcium Edthamil Disodium (CaEDTA) with relief of the acute gastrointestinal symptoms on each occasion; but he continued to complain of dizziness, headache, irritability, insomnia, decreased memory and decreased sexual drive. Six months after the onset of symptoms he had an acute onset of right sided paralyses, diagnosed as a stroke in a community hospital. He had a slow, progressive improvement over a twenty-six day hospitalization which left him with only mild residual right sided weakness.

Six months after the stroke, he had not returned to work and was admitted to the University of California, Los Angeles (UCLA) Medical Center for evaluation of persistent headaches, irritability, decreased memory and insomnia. On neurologic examination the only positive finding was mild right sided weakness. Laboratory examination revealed the following:

Blood lead: 34 µg/100 ml

Urine: 24-hr Coproporphyrin (COPRO) - 75 µg total volume (T.V.) 1411 ml

24-hr ALA - 1.4 mg T.V. 700 ml

24-hr lead - 35 µg T.V. 1070 ml

24-hr post chelation lead - 400 µg liter

EMG: Decreased voluntary motor units on right side consistent with right sided stroke; denervation potentials in small hand muscles. Nerve conduction studies within normal limits.

Other studies were within normal limits.

The second case is a forty-one year old man who worked in a secondary lead smelter for one year before developing constipation, abdominal pain, dizziness, nausea, and vomiting. These symptoms were relieved with a course of CaEDTA; but, after returning to work, he began complaining of generalized weakness, incoordination, intermittent dizziness, personality change and impaired mental functioning. During this period of time his blood lead ranged from 70 to 100 µg/100 ml. He quit work and was treated by a private physician with 10 iv infusions of 1g CaEDTA over the next five months. The 24-hour urine lead after the first CaEDTA infusion was 2631 µg and after the last 390 µg.

Because of persistent symptoms despite treatment, he was referred to UCLA Medical Center for further evaluation five months after quitting work. The only positive finding on neurologic examination was mild diffuse weakness most prominent in wrist extensors. Laboratory data were as follows:

Blood lead: 23 µg/100 ml

Urine: 24-hr COPRO - 190 g T.V. 3740 ml

24-hr ALA - 1.0 mg T.V. 1910 ml

24-hr lead - 12 µg liter

EMG: Radial nerves could not be stimulated on either side. Decreased motor units in hand muscles bilaterally.

Other studies were within normal limits.

The final case is a 26-year old man who worked in a secondary lead smelter for 1-1/2 years before developing fatigue, generalized weakness, constipation, crampy abdominal pain, nausea, headache, irritability and insomnia. During this period of time his blood lead ranged 100 to 190 µg/100 ml. He received two courses of treatment with CaEDTA (dose not known) with prompt relief of acute symptoms on each occasion. He did not return to work after the second course, however, because of persistent headaches,

fatigue, irritability and insomnia.

Three months later he was referred to UCLA Medical Center for evaluation of these chronic symptoms and additional complaints of personality change, impaired memory, decreased sex interest and intermittent chest pain. Neurologic examination was entirely within normal limits. His laboratory data were as follows:

Blood lead: 51 µg/100 ml

Urine: 24-hr COPRO - 95 µg T.V. 1580 ml

24-hr ALA - 1.0 mg T.V. 1580 ml

24-hr lead - 63 µg liter

24-hr post chelation lead - 674 µg liter

Complete Physical Examination: 3x upper normal

EKG: Nonspecific T and ST changes

Other studies were within normal limits.

These cases have several common features that deserve comment. Each patient had at least one bout of typical acute lead poisoning, manifested by severe gastrointestinal symptoms and milder nonspecific nervous system symptoms. In each case, the gastrointestinal symptoms promptly responded to chelation therapy, but the nervous system symptoms persisted and ultimately resulted in referral to the Medical Center. At the time of hospitalization, each patient had been removed from exposure for several months and there was little remaining laboratory evidence of increased lead absorption, including 24-hour post chelation lead excretion.

Unlike children, adults rarely develop prominent central nervous system symptoms as part of the acute lead poisoning syndrome.[1] However, as in these three cases reported, chronic complaints such as irritability, personality change, headache and insomnia are common. There are at least two reasons for this difference between adult and childhood lead poisoning; differing susceptability and differing rates of exposure.

The difference between acute and chronic exposure was demonstrated by Fullerton[2] when she produced death from cerebral edema in guinea pigs given a single massive dose of lead salt whereas, larger amounts spread out over weeks produced chronic wasting and weakness with wide spread motor nerve demyelination. In general, children with lead based paint ingestion have a much more acute exposure than adult lead workers.[3] A single paint chip can contain 1000 times the maximum daily permissable intake for a two-year old child.[4] A comparable degree of exposure in adults would be rare.

The developing nervous system is more sensitive to the damaging effects of lead than the mature nervous system.[5-6] This point is clearly demonstrated by the difficulty research pathologists have had in producing lead encephalopathy in adult animals.[7] Large doses of lead salts can be given to adult females of several species producing severe encephalopathy in their weaning young with little observable effects on the mother. In a recent report of brain uptake of radioactive labeled lead in adult and suckling rats, Goldstein, Asbury, and Diamond[8] found that brain uptake of lead in adults peaked after a week of chronic lead ingestion, whereas, the infants had a steady increase in brain lead concentration until they developed a fatal lead encephalopathy at four weeks of age. They also observed that CaEDTA could not remove lead that has already entered the nervous system of adults or infants. Similar results were obtained *in vitro* where the addition of CaEDTA did not remove lead bound to brain mitochondria.

Patient 1 had an apparent cerebral vascular thrombosis at age 50, without a previous history of hypertension or vascular disease. Although strokes are not a reported feature of either acute or chronic adult lead poisoning, there have been epidemiologic studies suggesting an increased incidence of strokes in lead workers compared to age-matched controls.[9] These studies were based on analyses of death certificates of former lead workers, most of whom had been heavily exposed during the early part of this century. A more recent study reported by Malcolm[10] of lead workers who died between 1963-1967, could find no increased incidence of cerebral vascular disease, suggesting that improved hygienic procedures beginning in the 1930's had paid off in improved worker survival. Because of the usual difficulties involved in retrospective studies of this type, however, the relationship between increased lead absorption and cerebral vascular disease is not settled.

The impaired nerve conduction and EMG findings in the second patient suggested chronic peripheral nerve damage consistent with his complaint of generalized weakness and the finding of wrist extensor on neurologic examination. There have been several recent reports suggesting physiologic abnormalities of peripheral nerves are common in lead workers.[11-12-13] Seppalainen and Hernberg[12] compared nerve conduction velocities in 39 lead workers with thirty-nine age-matched controls and found a significantly decreased nerve conduction velocity in the lead workers. In this original study, thirty-one of the thirty-nine lead workers had clinical lead poisoning and most had blood lead levels greater than 80 µg/100 ml.

As a follow-up study, Seppalainen and Hernberg[13] studied twenty-eight employees of a storage battery factory where worker exposure had been carefully monitored with frequent medical check-ups and blood lead determinations. They chose only workers who were asymtomatic and whose blood lead levels never exceeded 70 µg/100 m. These workers, along with an equal number of age and sex matched control subjects, were tested using

several nerve conduction measurements. As in the case of the earlier group with more severe exposure, the second group also showed a statistically significant slowing of the median and ulnar nerve maximum motor nerve conduction velocities. Even more significant were the decreased conduction velocity of slower conducting fibers, a new, apparently more sensitive, test developed by Seppalainen. On questioning, a few of these workers complained of paresthetic feelings and tiredness of the legs but none required sick leave for these symptoms. Of particular concern, in Seppalainen's preliminary observations is the suggestion that these measurable electrophysiologic abnormalities are not reversible. The continued impaired nerve conduction in the second patient, despite multiple injections of CaEDTA and months of removal from lead exposure, would support these observations.

Although there are isolated reports of significant improvement in lead induced motor neuron disease and peripheral neuropathy after treatment with chelation therapy,[14-15] most studies have not been encouraging, and in the case of motor neuron disease, death has occurred despite adequate chelation treatment.[16]

All of this data reinforces a disturbing clinical impression that nervous system damage from increased lead absorption is only partially, reversible, if at all, with chelation therapy and/or removal from further exposure. This is not particularly surprising, however, since experience with other heavy metal intoxication has been similar. Nervous system damage from arsenic and mercury responds minimally to chelation therapy.[17-18-19] Apparently, irreversible changes occur once the heavy metal is bound by nervous tissue. Although further study is clearly needed, the major point I would like to make this morning is that there is strong evidence to suggest the only reliable way to treat nervous system damage from increased lead absorption is to prevent its occurrence in the first place.

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MODERATOR-Dr. Jaroslav Vostal

Thank you Dr. Baloh for your interesting discussion. We must get on with the session for we still have one presentation before the coffee break.

The behavioral effects of lead intoxication cannot be disassociated from the neurological symptomatology of the central nervous system, and Dr. John Repko, Assistant Professor and Acting Director of the Performance Research Laboratory at the University of Louisville, will address himself to this question. Dr. Repko.

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