MISSISSIPPI MEDICAL CENTER
2500 North State Street
JACKSON 6, MISSISSIPPI

Area Code 601
362-4411

School of Medicine
Department of Medicine
Division of Neurology

1 March 1968

Robert A. Kehoe, M. D.
Professor Emeritus of Occupational Medicine
Kettering Laboratory
College of Medicine
University of Cincinnati
Eden Avenue
Cincinnati, Ohio 45219

Dear Dr. Kehoe:

Enclosed is a report of the studies we have done on patients with amyotrophic lateral sclerosis concerning which we have been in correspondence with you for the last several years. We would appreciate your reading the paper and giving us the benefits of any comments you might have on it. We are particularly interested in your comments on what we have said about the normal levels quoted by most laboratories for lead and mercury as discussed on pages 5 and 6 of the text.

We wonder if what we have said is correct. We certainly appreciate your helping us by reading this paper and will look forward to any comments you may have on it.

With kindest regards, I am

Yours sincerely,

Robert D. Currier, M. D.

RDC/lh

Amyotrophic Lateral Sclerosis and Metallic Toxins

by

Robert D. Currier and Armin F. Haerer

In a recent survey of amyotrophic lateral sclerosis (ALS) and multiple sclerosis in Mississippi[1] it was noted that amyotrophic lateral sclerosis was more common in persons who had engaged in heavy physical labor, particularly farming. As a consequence of and in addition to the history of heavy labor an apparently disproportionate number appeared to have been exposed to metal-containing toxins in their work.

References regarding a possible relationship between metal toxicity and amyotrophy can be found in the literature dating back to the work of Wilson in 1907[2] who reported ALS-like amyotrophy from chronic lead poisoning. Chronic mercurialism in farmers was incriminated by Brown[3] as a possible cause for a syndrome resembling ALS. Kantarjian[4] more recently described a similar syndrome which followed poisoning by ingestion of mercurials. There do not appear to be any reports of an acute or delayed amyotrophic syndrome as a consequence of exposure to gold, silver, zinc or arsenic. However, no detailed investigation of chronic or acute intoxication by heavy

---

From the Division of Neurology, Department of Medicine, Univ. of Mississippi Medical Center, Jackson, Mississippi, 39216.

Partially supported by NIH grants NBO 5215 and FR 00091.

Read in part at the 2nd Pan American Congress of Neurology; 1967, San Juan, Puerto Rico.

metal compounds or arsenicals as a possible cause of clinically typical ALS appears to have been undertaken. Heavy metal analyses on tissues from such patients have not been reported in detail, possibly because reliable methods for testing are of ~~more~~ recent development.

Because of the frequent positive history of exposure to substances containing metallic compounds in the present series of patients with ALS it was felt that a systematic search for traces of these substances in the urine and tissues might be worthwhile and that empirical therapeutic trials with various chelating agents might be justified, even though there might not be increased concentrations of these metals in the body fluids.

Reports by Steinke[5] and others have hinted that an association may exist between ALS and abnormal carbohydrate metabolism. Pyruvate represents a focal point in intracellular carbohydrate metabolism which may be deranged as well in some metal intoxications, notably arsenic, but also in lead and mercury poisoning to some degree. Since a possible abnormality of carbohydrate metabolism might therefore exist in ALS patients due to metal exposure, the serum and cerebrospinal fluid pyruvate in a portion of the present group of patients was also investigated.

Methods

Over a four year period (1962-1966) 31 patients were examined and found to have definite ALS and were thus included in this series. The toxicity studies omit 10 of the 31 because no specimens were obtained for various reasons.

Detailed histories were obtained with special emphasis on exposure to metals, and neurologic examinations were done on all patients. The

usual baseline investigations for establishing the diagnosis of ALS beyond reasonable doubt were carried out, including x-rays, electromyography, cerebrospinal fluid examinations, etc.

Analyses for lead, mercury and arsenic were done on 24 hour urine specimens that had been collected so that the urine never touched metal and that were stored in washed metal-free containers. Three laboratories employing different methods performed the analyses. Bio-Science Laboratories of Van Nuys, California used a modification of Hubbard's method[6] for mercury analysis, their own unpublished method for analysis of lead, and a spectrophotometric method for the determination of arsenic. The Third United States Army Medical Laboratory at Fort McPherson, Georgia used a modification of the method of Cholak[7] for lead determination and the mercury determination method of Nobel and Nobel.[8] The methods used by the Mississippi State Chemical Laboratory were those of Elkins[9] and the Chemical Rubber Company.

Therapeutic courses of versenate, penicillamine and thioctic (lipoic) acid were given to several patients. The details are described under results.

Lead and mercury analyses on autopsy tissues were performed by the Kettering Laboratory of Cincinnati (Drs. Kehoe and Tepper).

Results

A total of 31 patients with definite ALS were studied. An additional 15 patients with probable, rather than definite ALS in whom the history and results were similar were also studied but will not be reported in detail at this time. The majority of the patients listed in Table 1 were males as is true in most other series. The division between whites and Negroes corresponded to the population distribution in the state of

Mississippi (58% white). The age of onset (54 years) and duration of disease (3 years) correspond well with those of other series. None of the patients had significant abnormalities on x-rays of the spine and skull. Eighteen of the 31 were studied with electromyography which in all cases was consistent with ALS. The cerebrospinal fluid was normal in 23 patients and showed a slight increase in protein in five. Three patients had myelograms which were normal. Postmortem examinations on 7 patients were consistent grossly and microscopically with a diagnosis of ALS.

Table 2 summarizes the occupational data. Ten patients were full-time farmers growing cotton and other crops. Eight other patients were part-time farmers. Thirteen performed non-farming heavy manual labor throughout most of their lives. Seven patients had occupations with only slight or moderate physical exertion, and several others did part-time work involving heavy physical labor. There is obviously some overlap between these groups.

Table 3 details the history of exposure to toxic agents. Sixteen patients, about half, had a definite prolonged exposure to toxic materials. Nine of these were exposed to sprays and/or compounds used in treating cotton seed (seed disinfectants) which contained various mercurial compounds. Five of the 16 worked with substances containing lead and two were exposed to other metals. In addition, ten other patients had probable exposure to metals as listed under II in this Table. Seven patients had no definite history of exposure to toxic agents or the history was uncertain. Several patients had more than one type of exposure.

Metal determinations. Table 4 summarizes the concentrations of lead, mercury and arsenic in urines of the patients before treatment with

chelating agents. Six arsenic determinations, 20 lead determinations, and 15 mercury determinations were done. The average concentrations in micrograms per liter of urine are listed with the range in micrograms per liter and the number of patients who showed excretions above the "normal" limit given by the laboratories. There were two patients with elevated urinary lead concentrations and one with an elevated urinary mercury concentration.

Table 5 compares the heavy metal excretions of patients with a positive exposure history to the excretions of those who were not exposed. For arsenic, there were no values above the "normal" upper limits in the urines of patients with or without a history of exposure. Two patients had slightly elevated urinary lead concentrations, one of whom had a positive exposure history and one who did not give such a history. The one patient with elevated mercury values stated that he had not been exposed to any mercurial compound. In all patients with a history of exposure with four exceptions (patients #1, 22, 28 and 30, Table 6) the exposure had continued until the onset of the disease. The urine sample was obtained during the usual diagnostic hospitalization period at an average time of one year after onset.

Table 6 summarizes the exposure history, treatment regimens and metal determinations in all exposed patients.

Thus, it appears that although there is frequently a history of exposure these substances are not often present in abnormal amounts in 24 hour urine specimens and there appears to be no correlation of the history of exposure to the amount of toxin found.

It can be seen that the laboratories give different values for the upper limits of normal for heavy metals in the urine. In the present study each value is considered normal or abnormal in relation to the

figures given by the laboratory performing the test.

However it must be remembered that upper limits of normal for these elements are related to levels set with consideration of the possible production of symptoms in patients with a history of known exposure.

The true normal excretions of lead and mercury in non-exposed persons are considerably lower; lead being 32 μg/L urine (S.D. ± 10 μg)[10] and the total daily output of mercury in the urine being 10 to 50 μg.[11]

Hilf and Castano[12] state that "because of the discrepancy in the literature as to the normal urinary lead content we have assumed that any urine containing more than 50 micrograms of lead per liter is worthy of notation." In the light of this comment, it might be pointed out that there were five different patients before treatment in our series with one or more values each that exceeded 50 micrograms of lead per liter of urine.

Pyruvate studies. Studies of the blood pyruvate concentration on fasting specimens were done on five patients and spinal fluid pyruvate was measured in 7 patients. These were all within the normal ranges.

Treatment. It was felt that perhaps a single urinary 24 hour sampling for arsenic, lead or mercury might not reflect adequately the body stores of these substances. For this reason, and since ALS is a relentlessly progressive disease it was decided that treatment with chelating agents might be worthwhile. Five patients received therapeutic courses of versenate, four received penicillamine and three received thioctic (lipoic) acid. Of those patients with consistently normal lead levels before treatment, urinary lead concentrations rose after treatment in three cases, fell in two, but remained "normal" at all times. Of the two patients with lead values above "normal", the level dropped to normal before treatment in one, and treatment did not change it. The other

patient's lead value dropped after treatment. The patient who had elevated mercury levels showed a lower urinary concentration a few days after treatment, but the concentration had risen almost to the pretreatment level 3 months later.

In none of the patients did the treatment appear to change the course of the disease.

Post mortem studies. Tissues obtained at autopsy from 2 patients of the group were sent for lead and mercury analyses to the Kettering Laboratory. One of these patients had no exposure to heavy metals but the other had a definite history of exposure to various cotton poisons on several occasions. Both had normal amounts of heavy metals in their urines done prior to death and both had pathologically verified ALS. Analysis of spinal cord, liver, and kidney in one, and bone, brain, liver, kidney and spinal cord in the other patient revealed normal concentrations of lead and mercury with the exception of a slightly increased amount of mercury in one patient's kidneys. This was interpreted as possibly secondary to administration of a mercurial diuretic, although there was no definite history that the patient ever had been so treated. It should be noted that one patient had been treated with thioctic acid and versenate and the other with penicillamine.

Discussion

It appears that no correlation can be made between the amount of lead and mercury in any of these patients' tissues and their ALS.

The normal amounts of pyruvate in the blood and spinal fluids would tend only to rule out acute arsenic or heavy metal intoxication since the pyruvate does not remain elevated for long after these toxins are removed.

The possibility must be considered that exposure to heavy metals or

arsenic at an earlier time in life may then or later initiate a process of abiotrophy which becomes evident clinically at a time when pathologic concentrations of such substances are no longer detectable in the body fluids or tissues. It appears difficult to prove or disprove this at the present time. This is especially pertinent since the present studies were obtained from one to 20 years after contact with the possibly toxic substances. It thus is not unexpected that most of the evidence had disappeared if indeed it had ever existed. Perhaps study of tissues from patients with fulminating ALS or of some who died early in their disease from unrelated causes might give added information.

The changes in lead and mercury concentrations following the therapeutic trials do not seem to present any consistent pattern.

It can be concluded from the present data that no relationship has been shown between exposure to the substances analyzed and amyotrophic lateral sclerosis in this patient group.

Summary

The majority in this series of 31 patients with ALS had been exposed to metallic toxins in their work but no convincing evidence could be found of abnormal amounts of lead, mercury or arsenic in their urine or in necropsy tissues.

Bibliography

1. Breland, A. E., and Currier, R. D.: Multiple sclerosis and amyotrophic lateral sclerosis in Mississippi. Neurology, 17:1011/1016, 1967.

2. Wilson, S. A. K.: The amyotrophy of chronic lead poisoning: Amyotrophic lateral sclerosis of toxic origin. Rev. Neurol. & Psychiat., 5:441, 1907.

3. Brown, I. A.: Chronic mercurialism: A cause of the clinical syndrome of amyotrophic lateral sclerosis. Arch. Neurol. & Psychiat., 72:674, 1954.

4. Kantarjian, A. D.: A syndrome clinically resembling amyotrophic lateral sclerosis following chronic mercurialism. Neurology, 11:639, 1961.

5. Steinke, J., and Tyler, H. R.: The association of amyotrophic lateral sclerosis (motor neuron disease) and carbohydrate intolerance, a clinical study. Metabolism, 13:1376, 1964.

6. Hubbard, D. N.: Determination of mercury in urine. Anal. Chem., 12:768, 1940.

7. Cholak, J., Hubbard, D. N., and Burkey, R. E.: The determination of lead in freshly voided urine. A rapid screening test. J. Ind. Hyg. & Tox., 30:59, 1948.

8. Nobel, S., and Nobel, D.: Determination of mercury in urine. Clin. Chem., 4:150, 1958.

9. Elkins, H. B.: The Chemistry of Industrial Toxicology, 1950, John Wiley & Sons, Inc., New York.

10. Kehoe, R. A.: The metabolism of lead in man in health and disease. The Harben Lectures, 1960. J. of the Royal Institute of

Public Health and Hygiene, 1961.

11. Polson, C. J. and Tattersall, R. N.: Clinical Toxicology, 1969, J. B. Lippincott Co., Philadelphia.

12. Hilf, R., and Castano, F. F.: A simplified method of determination of urinary lead. Clin. Chem., 9:163, 1963.

TABLE 1

ALS Series, General Data

Total patients	31
Males	26
Whites	19
Negroes	12
Onset of disease, age	25-76
Duration of disease, average years	3 (range 1-8)
Spine x-rays normal	24
Spine x-rays mild degenerative changes	4
Electromyography done and compatible with ALS	18
CSF normal	23
CSF protein slightly up	5
Postmortems done (ALS proven)	7

TABLE 2

Occupational Data, Patients with A.L.S.
(31 patients)

Primary Occupation	# of Patients	Secondary Occupation, if any
Farmer (cotton chiefly)	10	Part-time Farmer Railroad worker Minister
Manual Heavy Labor (not farming)	13	Painter Secretary Dental technician Service station attendant Welder
Factory worker (2) Electrician (1) Meat packer (1) Athlete (1) Welder (2) Carpenter (1) Painter (2) Cook (1) Construction (1) Wood work (1)		
Other Occupations	7	
X-ray technician (1) Housewife (4) Registered nurse (1) Barber (1)		
Unknown	1	

TABLE 3

History of Exposure to Toxic Agents, Patients with A.L.S.
(31 patients)

	Number of patients
I. Definite exposure by history	
Cotton sprays and/or treated seeds	9
Lead (soldering, welding, and painting	5
Silver (x-ray developer)	1
Various metals (amalgams, etc.)	1
Total	16
II. Probable exposure by history	
Cotton sprays and/or treated seeds	6
Lead (paint, etc.)	4
Total	10
III. No definite history of exposure to toxic agents, or unknown	7

(NOTE: Totals exceed total number of patients, as several had more than one type of exposure.)

TABLE 4

Excretions of heavy metals (before treatment) of all patients with ALS tested

	Arsenic	Lead	Mercury
# Patients	6	20	15
µg/L urine excreted, average	5	37	23*
range, µg/L	0-30	0-212	0-365*
number above "normal" limits	0	2	1

* All but one were below 20 µg/L

TABLE 5

Heavy metal excretions of patients with and without history of exposure to each metal

	Arsenic		Lead		Mercury	
	Exposed	Not Exposed	Exposed	Not Exposed	Exposed	Not
# Patients	4	2	7	13	4	
Average urinary levels, µg/L	0.7	5	42	39	4	
Range, µg/L	0-3	0-10	0-205	0-212	0-17	0
# Patients above "normal" limits for tests	0	0	1	1	0	