NEUROFIBRILLARY CHANGES FOLLOWING CHILDHOOD LEAD ENCEPHALOPATHY

CASE REPORT

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ABSTRACT

This report details the findings in a patient who survived severe lead encephalopathy at age 2½ years, to die 42 years later in a state of severe mental deterioration. The brain revealed diffuse cortical atrophy, most severe in the temporal lobes, followed by hippocampi, amygdaloid nuclei and frontal cortex. Numerous pyramidal cells of the forebrain grisea contained Alzheimer’s neurofibrillary tangles. The remaining pyramidal cells of the hippocampi exhibited granulo-vacuolar degeneration. Many senile plaques were present predominantly in the atrophic temporal cortex.

Electron microscopic examination revealed many 800 Å twisted tubules in the tangles.

Atomic absorption spectrophotometry disclosed a tenfold increase of lead in frontal and temporal cortices as compared to suitable controls.

The possibility that toxic levels of lead in any form could result in the formation of Alzheimer’s fibrillary tangles is discussed.

INTRODUCTION

Most lead compounds represent a well known health hazard, not only to man but to all mammals. Lead can affect many organ systems and produces hematological, gastrointestinal and neurological symptoms (7, 12, 13). Damage to the central nervous system is of particular significance. Children up to four years of age are affected preferentially (1, 2, 8, 17, 32) and may develop lead encephalopathy, which is often fatal. Those who survive usually present neurologic problems such as learning disabilities, memory defects and seizure disorders (3, 13, 14, 24). Although the pathology of lead encephalopathy is well documented, only acute cases are on record (1, 5, 23, 25).

The following report concerns a patient who survived a childhood lead encephalopathy no less than forty years, suffering from a progressive mental deterioration. Neuropathologic examination revealed diffuse cortical atrophy with, as a fascinating hallmark, innumerable neurofibrillary tangles throughout the forebrain grisea, and also granulo-vacuolar changes in the pyramidal cells of the hippocampus.

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CASE REPORT

Clinical History: F.W. was born in October, 1928. Birth and development up to two years of age were normal. At age 2½ years the child began to behave peculiarly, cried abnormally and displayed increased irritability alternating with periods of drowsiness during which he talked less distinctly. The child vomited frequently and complained of abdominal pain. In September and October, 1931 and twice in July 1931, generalized convulsions were observed. The child was admitted to Children's Hospital in Cincinnati in July 1931 with signs of severe progressive mental and physical deterioration.

The patient's father was a painting contractor, in whose home large quantities of different paints were stored, to which the child had easy access. On many occasions his hands and mouth were covered with paint. Furthermore, the child used to chew lacquer and lead paint film from furniture. Spells of chewing paint (pica) date back approximately to the time the child was one year of age.

The neurological examination revealed dilated and fixed pupils. Deep tendon and abdominal reflexes were absent. Movements of the hands were slow and associated with a slight tremor. The legs were quite weak. Peripheral chorioidal patches of pigment accumulation indicated a low grade toxic choroiditis.

Laboratory findings: Marked basophilic stippling of the red blood cells was present. X-rays of the skull were normal, but the long bones showed moderate increased density along the epiphyseal lines. Lead (Pb) levels of urine and stool were determined. Although the actual values are no longer available, the patient's chart reports consistent and significant elevations.

Diagnosis: Chronic plumbism with lead encephalopathy.

Treatment consisted of calcium lactate, ferrum reductum and sodium biphosphate. The symptoms of acute intoxication gradually cleared and the child was discharged from the hospital in October, 1931. The boy did not talk again until five years old, when a slowly progressive mental retardation commenced. During the following years, occasional grand mal attacks and minor seizures occurred, usually in the spring. In 1933, the patient became increasingly moody, with irritability culminating in tantrums. After a series of recurrent, severe seizures, he was permanently institutionalized in 1954, at age 26 years.

In November, 1972, following an acute rectal hemorrhage, a papillary adenocarcinoma was found 6 cm above the anal ring. After abdominal perineal resection on November 30, the patient developed fever. Death resulted from bilateral lower lobe pneumonia 27 days later. The patient was 44 years old.

The autopsy revealed no residual carcinoma, but bilateral lower lobe pneumonia and a right lobe pulmonary infarction.

Gross Description of the Brain. The brain weighed 1,000 gm. The leptomeninges showed minimal thickening. The major vessels at the base appeared normal. The gyri of both hemispheres were narrow and the sulci wide and gaping, more so in the temporal lobes. The occipito-parietal cortex appeared best preserved. No gross changes were found in brain stem and cerebellum.

Coronal sectioning revealed narrowing of the cortex and shrinkage and grayish discoloration of the white matter of both temporal lobes (Fig. 1). Both hippocampi were whitish, firm and slightly shrunken. Although the basal ganglia appeared well preserved, the deep white matter was generally reduced in extent. Widening of the lateral and third ventricle was moderate, with the exception of the more severely dilated temporal horns. The substantia nigra was partly depigmented and appeared narrow. The cerebellar cortex showed areas of shrinkage with increased consistency, most pronounced over the posterior aspects of the right hemisphere. The vermis appeared normal.

Microscopic Description of the Brain

Representative sections revealed generalized cerebrocortical atrophy with the temporal poles most severely involved. Here, thickness of the cortex was dis-
Fig. 1. Coronal section. Atrophy of temporal lobes.

Fig. 2. Hippocampus. Remaining pyramidal cells in the resistant band (rb), cell loss in Sommer’s sector (ss), entorhinal area (es). Bodian stain; Loupe.
tinctly reduced and the cytoarchitecture was no longer discernible due to neuronal loss. Many of the remaining pyramidal cells contained neurofibrillary tangles, others harbored round argentophilic inclusions such as seen in Pick's disease. The white matter was rarefied with a marked loss of myelinated fibers. The amygdaloid nuclei also were atrophic with innumerable neurofibrillary tangles in the residual neurons. Diffuse astrocytic gliosis was present in gray and white matter.

The hippocampi revealed an almost total loss of pyramidal cells in the endolium and Sommer's sector (Fig. 2). Whereas the remaining pyramidal cells of Spielmeyer's resistant band exhibited granulo-vacuolar degeneration (Fig. 3), those of the entorhinal cortex contained predominantly fibrillary tangles (Fig. 4). The granule cells of the dentate gyrus appeared unaffected.

Other cortical areas displayed neuronal loss and neurofibrillary tangles to a lesser degree. Although the visual cortex was normal, areas 17 and 19 contained occasional neurofibrillary tangles. In summary, cortical atrophy affected the temporal, parietal, frontal and occipital cortices in that order of severity.

Scattered small senile plaques were found throughout the forebrain grisea, but they were quite frequent in the cortex of the temporal lobes.

In the cerebellum, symmetrical, rather sharply demarcated areas of cortical sclerosis were found. The affected folia were shrunken due to a complete loss of Purkinje cells, a significant decrease in the number of granule cells, and loss of myelinated fibers with astrocytic gliosis. The preserved portions of the cerebellum contained occasional swollen axons.

The cerebral vasculature was well preserved except for an occasional mineralized capillary in the atrophic posterior-inferior portion of the cerebellar cortex and in the globus pallidus.

**Electron Microscopy**

Pieces of temporal cortex, previously fixed and stored in formalin, were post-fixed in 2% OsO₄ buffered with cacodylate and further processed for electron microscopic examination (21). Despite the extended formalin fixation and storage, the ultrastructure of the neurofibrillary tangles was well preserved. Two types of neurofibrillary arrangements within the perikarya could be identified. The first consisted of tubules, arranged in compact bundles and surrounded by an outer limiting membrane (Fig. 6). The second was characterized by more diffusely distributed tubules, (Fig. 7). Whereas the tubules of the first type consisted mostly of straight 200 Å tubules, the second contained mostly 800 Å twisted tubules, measuring 200 to 220 Å in width and 100 Å in the twisted portion (Fig. 5).

**Lead and Aluminum Analysis**

Samples of representative areas of the brain were dry-ashed and dissolved in acid. Lead (Pb) and aluminum (Al) were measured by atomic absorption spectrophotometry (Perkin-Elmer Model 403). For comparison, comparable areas of other brains, stored and processed similarly, were assayed. Additionally, the same procedures were applied to unfixed tissues from an acute childhood lead encephalopathy.
Fig. 3. Hippocampus. Pyramidal cells with granulo-vacuolar degeneration in the Spielmeyer resistant band. Bodian stain; × 1000.

Fig. 4. Hippocampus. Pyramidal cell with Alzheimer's neurofibrillary tangles in the entorhinal area. Bodian stain; × 1000.

Fig. 5. Longitudinal section of 800 Å twisted tubules displaying the periodic constriction (arrows); × 87,000.
Fig. 6. Longitudinal section of a bundle of straight tubules with limiting membrane (m); × 38,000.
Fig. 7. Part of a neurofibrillary tangle of a pyramidal cell of the temporal lobe with longitudinal twisted tubules (arrows) and cross sectioned tubules of circular and arcuate form (bottom); × 38,000.
TABLE I

Brain Tissue Levels of Pb and Al in Human Autopsy Material Expressed in μg Per Gram Wet Weight

<table>
<thead>
<tr>
<th>No.</th>
<th>Patient</th>
<th>Age in Years</th>
<th>Diagnosis</th>
<th>Frontal Cortex</th>
<th>Temporal Lobes</th>
<th>Hippocampus</th>
<th>Cerebellum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pb</td>
<td>Al</td>
<td>Pb</td>
<td>Al</td>
</tr>
<tr>
<td>1</td>
<td>NP72-120</td>
<td>44</td>
<td>Present Case*</td>
<td>3.3</td>
<td>3.0</td>
<td>4.2</td>
<td>3.6</td>
</tr>
<tr>
<td>2</td>
<td>NP72-106</td>
<td>68</td>
<td>Alzheimer's Disease</td>
<td>0.3</td>
<td>2.2</td>
<td>0.5</td>
<td>2.2</td>
</tr>
<tr>
<td>3</td>
<td>U72-45</td>
<td>69</td>
<td>Recent Embolism, Hemorrhagic Infarct</td>
<td>0.4</td>
<td>1.7</td>
<td>0.5</td>
<td>2.1</td>
</tr>
<tr>
<td>4</td>
<td>VAN74-23</td>
<td>72</td>
<td>Congenital Spinal Malformation</td>
<td>0.1</td>
<td>1.0</td>
<td>0.4</td>
<td>1.7</td>
</tr>
<tr>
<td>5</td>
<td>4090/73</td>
<td>3</td>
<td>Lead Encephalopathy</td>
<td>2.1†</td>
<td>0.3†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Pb of the storage medium (formalin) < 0.05 μg/ml.
† Samples were taken from unidentified cortex.

As seen in Table I lead and aluminum were present in all brain samples. Whereas the Pb values of the hippocampus and the cerebellum of the chronic case were in the same range as those found in the controls, frontal and temporal cortices exhibited approximately a tenfold elevation. These levels are comparable to that of case 5, an acute childhood lead intoxication.

The concentrations of Al in all areas studied on the subject case were 50 to 100% higher than in the controls, with the highest levels present in the hippocampus.

Since cases 1–4 had been fixed and stored in formalin from 9 months to one year, the lead concentration of the formalin was determined and found to be less than 0.05 μg/ml. Therefore, it appears unlikely that prolonged formalin fixation and storage accounts for the increased levels of these metals; also, the distinctly different levels obtained for various areas of the same brains, argue against a significant degree of contamination.

DISCUSSION

The clinical history of the subject case, is to some degree superimposable with that of others who survived childhood lead encephalopathy for a prolonged period of time (1, 23, 25). Such extended survivals are now more frequently observed, as early diagnosis and efficient treatment have become available (4, 6, 9, 26). Among the many pertinent observations, the subject case seems to have exhibited a more severe degree of mental and physical retrogression. To our knowledge, this case represents the only long-term survivor of childhood lead encephalopathy on record with exhaustive neuropathological and toxicological studies.

In this context it appears useful to briefly consider the neuropathology of lead encephalopathy. Despite severe clinical manifestation, the neuropathological
examination often uncovers only minor or nonspecific lesions in the central and peripheral nervous system. Whatever these changes, they are more severe in children than in adults (1, 23, 25), and usually but not invariably consist of ischemic neuronal necrosis and endothelial swelling (23, 25). The lesions are usually disseminated, affecting brain stem, cerebellum, cortex and hippocampus in this order of severity.

The present study revealed an entirely different neuropathological syndrome. The brain was diffusely atrophic and numerous nerve cells contained Alzheimer's neurofibrillary tangles. Granulo-vacuolar degeneration was conspicuous in the remaining pyramidal cells of the hippocampus. Most severely affected were the temporal lobes, followed by hippocampi, amygdaloid nuclei and frontal cortex. Thus, in a long-term survivor of childhood lead encephalopathy, with still elevated Pb levels, not only the nature of the disease process but also its distribution differs from the pattern seen in the acute form of childhood lead encephalopathy. Whereas in the latter ischemic neuronal necrosis and swelling of the endothelial cells predominate, the former is characterized by degenerative neuronal changes and diffuse brain atrophy.

It should be pointed out that the hippocampal sclerosis probably resulted from ischemia, because its distributional pattern is more consistent with iatrogenic damage, rather than with a toxic process. Nevertheless, it is interesting to note that not only convulsant agents (3-acetylpyridine, methoxypridoxine) (19, 20) but also lead (Pb) (21) produces ischemic neuronal necrosis of hippocampal pyramidal cells prior to the onset of convulsions in experimental animals. The patchy cerebellar sclerosis raises similar questions as to its pathogenesis; it is well known as the result of iatrogenic damage but it is equally well documented that acute lead poisoning produces focal cerebellocortical nerve cell loss (1, 23, 25).

Of particular interest is the widespread occurrence of Alzheimer's neurofibrillary tangles.

Neurofibrillary changes have been described in a variety of neurological disorders (15, 27, 34). More recently, aluminum has been found to produce neurofibrillary tangles and subsequently it has been claimed that the concentration of this metal is elevated in the brains of patients with Alzheimer's disease, suggesting a pathogenetic relationship (10). Our analyses, like those of others did not confirm this finding (18, 29). Furthermore, experimental topical and systemic administration of alumina failed to produce neurofibrillary tangles with 800 Å twisted tubules (29, 33), so characteristic of Alzheimer's disease.

It, therefore, remains an interesting speculation to incriminate lead as a possible cause of the neurofibrillary tangles in the present case. Actually, acute tetraethyllead poisoning produces neurofibrillary tangles in pyramidal cells of the frontal cortex and the hippocampus in young adult rabbits within 12 hours (22). Although the tangles consist predominantly of straight tubules, a few 800 Å twisted tubules were found in two out of 16 animals.*

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ADDENDUM

After submission of this report, we became aware of a recent publication by Hess and Straub (Praxis, 63:177–183, 1974), who described a case of an adult male with Alzheimer's disease. This patient revealed a clinical history of chronic lead intoxication in the course of lead exposure during 30 years of work in a battery factory. The authors concluded that “despite a typical clinical picture, lead cannot be definitely incriminated for the terminal encephalopathy since post-mortem examination revealed Alzheimer's disease.”

REFERENCES


