Alzheimer’s Disease with Markedly Elevated Arsenic and Other Metals Masquerading as Organic Brain Syndrome and Affective Disorder

Mahlon D. Johnson1*, and Darinka Mileusnic-Polcham2

1Departments of Pathology, Division of Neuropathology, University of Rochester School of Medicine and Dentistry, Rochester, New York, USA
2Regional Forensic Center, Knoxville, TN, USA

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*Corresponding author: Mahlon D. Johnson, Dept. of Pathology and Laboratory Medicine, Univ. of Rochester Medical Center, 601 Elmwood Ave. Box 626, Rochester, NY 14623, USA, Tel: 01-585-276-3007; Fax: 01-585-273-1027; E-mail: mahlon.johnson@urmc.rochester.edu

Abstract

We present a patient who, based on the finding of markedly elevated serum arsenic (As) and aluminum (Al) in hair and nail clippings, was thought to have an organic brain syndrome and affective disorder. Autopsy evaluation revealed definite Alzheimer’s disease (AD).

Numerous studies have suggested a role for As, Al, lead (Pb), cadmium (Cd) and mercury (Hg) in the pathogenesis of AD but none have been convincingly implicated in the development of AD, particularly if the exposure is in adults. Largely unreported, is the effects of extremely high levels of all of these metals in one patient.

We report a patient with a unique history of variable exposures over approximately 33 years to As (5011 × NI), Al (84 × NI), Pb (4.6 × NL), Cd (3.8 × NI), Hg (4.6) who was thought to have organic brain syndrome but at autopsy was found to have severe AD. The literature of metal dyshomeostasis and AD is briefly reviewed.

Keywords: Alzheimer’s Disease; Arsenic; Organic Brain Syndrome

Introduction

The role of metals in the development of Alzheimer’s disease (AD) remains unproven and controversial [1–5]. Several studies have found high levels of aluminum (Al) arsenic (As), lead (Pb) or cadmium (Cd) in the blood, cerebrospinal fluid or brains of patients with cognitive impairment or AD [1–12]. In experimental studies, adult exposure to several metals have been shown to alter amyloid precursor protein synthesis or catabolism and, in some cases, been correlated with the development of AD pathology [1,2,5,10]. Numerous studies have suggested a role for As, Al, lead (Pb), cadmium (Cd) and mercury (Hg) in the pathogenesis of AD but none have been convincingly implicated in the development of AD, particularly if the exposure is in adults. Largely unreported, is the effects of extremely high levels of all of these metals in one patient.

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Case Report

Occupational history

In 1967, at age 23, this patient initially began work with the Department of Energy in the Southeastern United States. In the 1980s, he began work with the Department of Defense and Environmental Protection Agency, inspecting national nuclear facilities primarily in Oak Ridge National labs but was sent to many different installations including: Oak Ridge National laboratories, Los Alamos, Hanover; Portsmouth, OH; Richland, WA; and Savannah River, NC. He was also sent to Chernobyl, Russia during their nuclear emergency. His work included supervising nuclear waste site cleanups. His exposures included arsenic, mercury, aluminum, and lead, among many others.

The patient’s symptoms started around 1998 at age 54. These included forgetfulness, hallucinations, delusions, paranoia, potentially harmful agitation and depression. Two weeks after onset of symptoms, he was seen in an emergency room for a possible “GI bleed”, which according to his wife, this was part of his hallucinations. Psychological abnormalities were documented by the emergency room physicians and he was admitted. His condition deteriorated and he was admitted to a psychiatric hospital for care. Subsequently he was transferred from one extended care facility to another. Three years after presentation, the patient lost ability to walk and developed atrophy of the extremities without recovery. In 2008, he was given a diagnosis of organic brain syndrome with organic affective disorder. In 2001, he suddenly lost his upper extremity strength. He became bedridden with upper and lower extremity contractions and loss of the ability to communicate. No myoclonus was noted during this period. Documentation of any EEGs, nerve conduction studies or EMGs was not noted. In 2008, hair and nail clippings were analyzed using Induced Coupled Plasma Mass Spectroscopy (ICPMS), the state of the art technology for identifying metals in tissue at the t and found to have extremely high levels of arsenic, mercury, cadmium and lead. Unchallenged urine samples, without prior chelating agent treatment, were also sent to a toxicology laboratory for screening for heavy metals (Summarized in Table 1). Urinalysis revealed low levels of arsenic. Environmental Medicine and Clinical Metal Toxicology experts were consulted. Treatment with chelating agents was considered and recommended by one expert but due to the high tissue levels and advanced stage of cognitive decline, were not attempted. Per the family, there was no family history of dementia or neuropsychiatric disorder.

Methods

Sections of right and left superior frontal gyrus, right and left superior temporal gyrus, right and left inferior parietal lobule, left inferior parietal lobule, right and left hippocampus were evaluated with Bielschowsky stains, phospho -Tau and ubiquitin immunohistochemistry. Sections of the right and left superior frontal gyrus were also evaluated using beta amyloid precursor immunohistochemistry and Congo red stains.

The Bielschowsky stain was performed as described [13] using Ammoniacal Silver. For immunohistochemistry an antibody to phospho Tau: (Phospho-PHF-tau pSer202+Thr205) mouse

<table>
<thead>
<tr>
<th>Source</th>
<th>Patient</th>
<th>Normal range</th>
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<tbody>
<tr>
<td>Aluminum</td>
<td>Nails</td>
<td>420 µg/kg</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Hair</td>
<td>400,900 µg/kg</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Urine</td>
<td>490 µg/kg</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Hair</td>
<td>300 µg/kg</td>
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<tr>
<td>Lead</td>
<td>Hair</td>
<td>1,023 µg/kg</td>
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<tr>
<td>Mercury</td>
<td></td>
<td>1,853 µg/kg</td>
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</table>

Table 1: Metal concentrations in patient with AD.
monoclonal antibody (AT8) (Thermo Fisher 1:1000) and rabbit anti-ubiquitin polyclonal (1:300, Dako, Carpenteria CA).

For immunohistochemistry, each case was analyzed with monoclonal antibody to: 1) phosphoryl-Tau and streptavidin-biotin immunohistochemistry performed on DAKO automated immunostainers. For antigen retrieval, used with most antibodies, tissue sections were incubated in a thermostable chamber with 10X Reveal Decloaker (Biocare Medical, Concord CA) at 120-123 °C and pressure of 20-24 psi for 45 minutes.

Pathology

The autopsy was limited to the brain. There was no epidural or subdural hematoma. The Circle of Willis was anatomically normal without significant atherosclerosis. The leptomeninges were translucent and overall the leptomeninges reveal no subarachnoid hemorrhage. The cerebral hemispheres were symmetrical and showed severe right and left frontal lobe atrophy and moderate parietal and superior temporal lobe atrophy bilaterally. There was no notable atrophy in the occipital lobes, cerebellum or brain stem. Coronal sections revealed cortical thinning and atrophy in the frontal parietal and temporal lobes without contusions. The centrum semiovale displayed no infarctions. Extensive hydrocephalus ex-vacuo was noted. The caudate nucleus was symmetrically atrophied without lacunar infarctions. The hippocampi were atrophic. Horizontal sections of the cerebellum revealed no atrophy or focal lesions. Sections of the mesencephalon revealed a patent cerebral aqueduct and pigmentation of substantia nigra bilaterally. There were no focal lesions in the pons and medulla.

In the sections of right and left superior frontal gyrus there was severe neuronal loss and diffuse transcortical gliosis accompanied by subcortical gliosis. No Lewy-like bodies or Pick bodies are found. Bielschowsky stains reveal extensive neuritic plaque and neurofibrillary tangle formation with up to 129 neuritic plaques (Figure 1A) and 46 neurofibrillary tangles per 10 high power fields (Figure 1B). Rare, diffuse “cotton wool” plaques were suggested. The Congo red stain also reveals apple-green birefringence in superficial cortical blood vessels and classic neuritic plaques (Figure 1C). Ubiquitin immunohistochemistry revealed no Lewy bodies or threads but p-Tau immunohistochemistry reveals large numbers of tangles (Figure 1D). The sections of right and left superior temporal gyrus displayed no Lewy-like bodies. Bielschowsky stains revealed moderate to frequent neuritic plaque, scattered primitive plaque and neurofibrillary tangle formation with up to 70 neuritic plaques and 19 neurofibrillary tangles per 10 high power fields. Ubiquitin immunohistochemistry revealed no Lewy bodies or threads but p-Tau immunohistochemistry revealed large numbers of neurofibrillary tangles. In the parietal lobes, there was also gliosis and neuronal loss. Bielschowsky stains revealed moderate neuritic and primitive plaque and neurofibrillary tangle formation. Ubiquitin immunohistochemistry revealed no Lewy bodies or threads. Phospho-Tau immunohistochemistry again revealed large numbers of neurofibrillary tangles. There was mild gliosis in the right caudate and severe gliosis in the left caudate. There was neuronal loss, phospho-Tau and Bielschowsky staining neurofibrillary tangles and gliosis in the entorhinal cortex bilaterally but Bielschowsky stains show no Pick bodies. The hippocampus

Figure 1: Cortical lesions. Bielschowsky-stained sections of the frontal lobes revealed numerous neuritic plaques (A, arrow), neurofibrillary tangles (B, arrow), Congo red staining neuritic plaques (C, arrow) and phospho-Tau immunoreactive neurofibrillary tangles (D, arrow). Bielschowsky (A and B) Congo red (C) and phospho-Tau (D) (original magnification x200)
displayed numerous neurofibrillary tangles on Bielschowsky and p-Tau stains but not notable ubiquitin neurites. Sections from the occipital lobe were not taken. The sections of cerebellum revealed preservation of the Purkinje cells and dentate. The substantia nigra exhibited pigmentation without Lewy bodies or pigmented incontinence. Sections of the pons and medulla revealed no focal lesions. The final diagnosis was Alzheimer’s disease, CERAD, definite.

Discussion

The autopsy revealed changes of advanced Alzheimer’s disease. Despite frontal atrophy and gliosis in the caudate nuclei, the density of neuritic plaques and neurofibrillary tangles argues against frontotemporal lobar degeneration. Unfortunately, permission was not granted for removal of the spinal cord or peripheral nerves.

The role of metals in the development of AD has been controversial, in part due to the diversity of models used and difficulty establishing causality. A number of studies suggest a role for Al, Pb and As in the eventual development of AD after prenatal or neonatal exposure [1]. Nonetheless, the role of extensive exposure of metals in adulthood has not been established.

The role of arsenic in AD has not been extensively studied. Long-term exposure to As was associated with poor memory and executive function in [8,9,14]. Several studies suggest high cerebral levels of arsenic may contribute to cognitive dysfunction [15]. As also increases Tau phosphorylation and increases transcription of the amyloid protein precursor gene [15,16]. In addition, As alters amyloid precursor protein metabolism or catabolism increasing both APP and sAPPbeta levels and Aβeta [1,17].

Numerous studies have evaluated the role of aluminum (Al) in the development of AD. This has been encouraged by studies demonstrating aluminum in brains of patient with AD. In addition, dialysis patients with high levels develop acute dementia [18] and administration to the brains of rabbits produced cognitive deficits associated with neurofibrillary tangles [19]. Epidemiological studies in the UK found an association with Al and AD [11]. However, limited correlation was also found by others [12]. Mechanistically, Al may facilitate Tau aggregation [20] and appears to be associated with phospho-Tau in Al-induced tangles [21] and inhibit protein phosphatase 2, which dephosphorylates phospho-Tau [22].

Whether adult exposure to Pb contributes to the development of AD is equally uncertain. High levels of Pb in bone were found to be associated with poor cognitive function in elderly workers in one study [6] although serum Pb levels had no correlation with dementia in another [7]. Nonetheless, a recent study suggests Pb may increase APP levels in cells [23]. The role of Cadmium in development of AD is not established. However, it may alter accumulation of amyloid. For example, Cadmium increases amyloid precursor protein synthesis [18] and alters amyloid beta peptide membrane channel resulting in large aggregates of precipitation-prone amyloid in cells [24,25].

Collectively these studies raise the possibility that several metals may compromise cognitive function and possibly contribute to the development of AD. Nonetheless, in part, due to the rarity of such cases, few have evaluated the accumulative effects of high levels of several neurotoxic metals on the same patient.

The findings suggest the diagnosis of AD must be considered in any patient organic brain syndrome. It raises the possibility that various metals such as As may hasten the onset of AD.

Conflicts of Interest

The authors have no conflicts of interest to declare.

References


