Technetium-99m-HMPAO Brain SPECT Evaluation of Neurotoxicity Due to Manganese Toxicity

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We performed initial and follow-up regional cerebral blood flow (rCBF) studies using ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO) SPECT on a patient with manganese-induced central nervous system (CNS) neurotoxicity. **Methods:** The patient had a history of long-term exposure to manganese at the time of the first scan, while the follow-up scan was performed 9 mo after removal from the toxic environment. The patient's serum level of manganese was five- to tenfold greater than normal at the time of the initial rCBF brain SPECT scan. **Results:** The rCBF brain SPECT scan demonstrated significantly decreased rCBF in the right caudate nucleus and both thalami. A MRI scan obtained at the same time was normal. The follow-up rCBF brain SPECT scan was normal. **Conclusions:** This report supports the utilization of functional rCBF brain SPECT imaging to provide objective evidence of a function CNS abnormality due to neurotoxicity at an early clinical stage. Our results emphasize that rCBF brain SPECT may provide a confirmational test to support the diagnosis of neurotoxicity in the appropriate clinical setting.

Key Words: neurotoxicity; manganese; encephalopathy; SPECT; technetium-99m-HMPAO

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Long-term exposure to toxic substances is a common medical problem in industrialized countries. Human beings are exposed to over 53,000 different substances, including pesticides, drugs, food additives, cosmetics, commercial and industrial substances (*1*). The problem is common since nearly all trace elements or organic solvents are potentially toxic if ingested or inhaled at high enough levels for long enough time periods (*2*).

Central nervous system toxicity results in many various forms of cognitive and neurological dysfunction. Heavy metals such as cadmium have been shown to produce behavioral abnormalities (*3*). Organic solvent exposure is known to result in chronic toxic encephalopathy (*4–6*). Behavioral changes have been linked to lesions in the basal ganglia (*7*). A reduction in basal ganglia blood flow has been shown in patients with anoxic encephalopathy (*8*).

Neuropathologic changes due to chronic and acute exposures in the workplace are often difficult to diagnose due to nonspecific complaints (*9*). Subclinical neurotoxic effects of various chemicals may be overlooked or misdiagnosed due to ambiguity of the early presenting symptoms (*10*). Since the early onset of symptoms is often insidious and nonspecific, a sensitive means for detecting toxic encephalopathy at an early stage is desirable.

Morphologic neuroimaging using computed tomography (CT) or magnetic resonance imaging (MRI) is helpful in detecting late changes. Chronic lead exposure leading to cerebral and cerebellar calcification has been reported (*11*). Basal ganglial signal intensity alterations on MRI due to long-term total parenteral nutrition manganese administration has recently been reported (*12*).

A study of toxic encephalopathy due to exposure to organic solvents using the ^{133}Xe inhalation method showed a decrease in regional cerebral blood flow (rCBF) in the fronto-temporal areas (*13*). A PET study of a patient exposed to the solvent tetrabromoethane demonstrated decreased uptake of ^{18}F-fluorodeoxyglucose (FDG) in the right thalamus (*14*).

CASE REPORT

The patient is a 52-yr-old female with an occupational history of working on an assembly line in a manufacturing plant for 19 yr. In her daily work she was exposed to the oils, coolants, solvents, metals, fumes and vapors which permeated the work site. The patient initially complained to her local physician about insomnia, headaches and dizziness of approximately 1-yr duration. Over the following year she developed symptoms of fatigue, malaise, memory loss, mental confusion, distractibility, depression and cognitive decline, and was referred to this institution for further evaluation.

Neurological examinations at this institution detected a complex of symptoms including episodic numbness and tingling, dizziness, poor balance, athetoid posturing of her hands, unsteady movements of her extremities and a positive Rhomberg test. The

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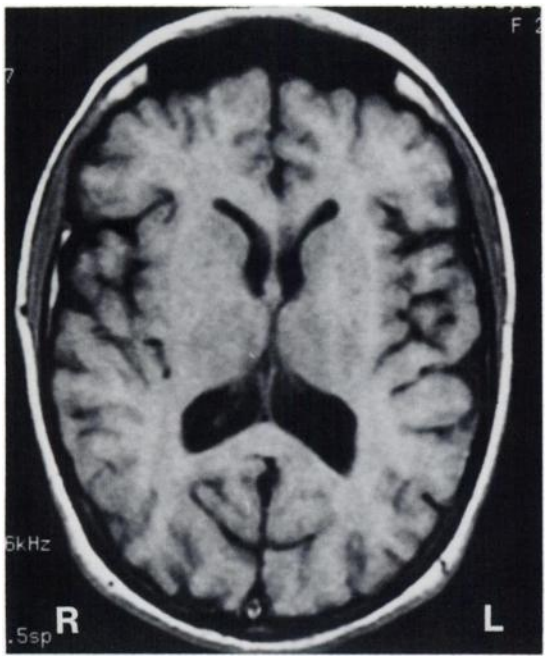

FIGURE 1. The MRI scan shows mild cerebral atrophy, but no abnormalities of the thalami or caudate head nuclei.

patient also revealed that these symptoms partially diminished when she was removed from the manufacturing plant for several weeks or more, but reoccurred when she returned to work.

The patient was referred to an environmental medicine clinic where she underwent a comprehensive occupational and environmental medical evaluation. An investigation into the working conditions revealed the presence of solvents containing manganese, lead, copper, zinc, nickel, cadmium, selenium, thallium and benzene fumes. The toxicology laboratory tests showed that the patient's serum level of manganese was 4.8 ng/ml (maximum normal range = 0.40–0.85 ng/ml). A brain MRI scan was performed for further evaluation. The scan showed mild nonspecific atrophy for age (Fig. 1) and the patient was advised to return to work. The patient's symptoms got worse, and a ^{99m}Tc-HMPAO brain SPECT scan was performed. The patient was not taking any medication at the time of imaging.

METHODS

The initial and follow-up rCBF brain SPECT scans were performed after the intravenous injection of 20 mCi ^{99m}Tc-HMPAO under the resting conditions with eyes closed in a dim, quiet room. Scanning was performed on an ADAC Genesys dual-head Anger gamma camera using 128 total stops, acquiring approximately 15 million total counts. Low-energy, parallel-hole, high-resolution collimators were employed yielding image resolution of approximately 8.5 mm full width at half maximum. The matrix size was 128 × 128 (pixel size of 1.96 mm). Image data was attenuated using the Chang method (*15*), and reconstruction was performed using a Butterworth filter with a frequency cutoff 0.225 Nyquist, order 6 (*16*). Image reconstruction and semiquantitative analysis was performed using the ADAC Pegasys workstation.

Transverse sections were reconstructed parallel to the canthomeatal line defined by the reference system routinely employed in the Division of Nuclear Medicine (*17,18*). Cortical circumferential profiles were obtained by delineating an annular ring of cortex 1.96 cm (10 pixels) wide using a computer-automated algorithm (*19,20*). The perimeter of this annulus was defined by a pixel threshold value of 50% of the average pixel value for the entire slice (*19,20*). Individual cortical regions were then created by subdividing this annulus into twelve sectors of equal angle. This was performed at canthomeatal CM + 3.5 cm, CM + 5.5 cm, and CM + 7.5 cm. Average counts-per-pixel in each cortical region of interest (ROI) were normalized to cerebellar counts, and compared with age- and sex-matched normal controls analyzed in the same manner using a computer-automated algorithm (*21*).

The thalamic and caudate uptake activity was determined by drawing ROIs around these structures on the MRI scan which were then transposed to the rCBF brain SPECT scan (*17,18*). Average counts per pixel in each subcortical ROI were normalized to cerebellar counts (Fig. 2).

RESULTS

The cortical region-to-cerebellar count ratios were within the normal range established at this institution (*21,22*). The subcortical nuclei region-to-cerebellar count ratios demonstrated marked diminution of tracer uptake in the caudate head nuclei (left caudate = 0.86, and right caudate = 0.76) with greater diminution in the thalami (left thalamus = 0.76, and right thalamus = 0.75) on the initial rCBF SPECT brain scan. Normal region-to-cerebellum values ± 1 s.d. determined by this institution are 0.96 ± 0.05 for the thalami and 0.94 ± 0.06 for the caudate head nuclei (*21,22*). Thus, compared to normal controls, the left caudate was approximately 2 s.d. below normal, and the right caudate and both thalami were approximately 3 s.d. below normal (Fig. 3A). The 1-yr follow-up rCBF SPECT scan showed all uptake values to be within 1 s.d. of the normal range (left caudate = 0.91, right caudate = 0.88; left thalamus = 0.92, right thalamus = 0.91), (Fig. 3B).

DISCUSSION

This report illustrates a markedly abnormal rCBF pattern in a patient who has been exposed to a variety of toxic substances for many years, and who had high serum levels of manganese. Toxic encephalopathy in this patient due to exposure to manganese and other chemicals was initially suspected by her abnormal clinical and toxicology analysis. Inspection of the manufacturing plant confirmed the presence of toxic agents. The suspicion of CNS toxicity was objectively supported by the transformation of the rCBF brain SPECT scan to normal after she was removed from the toxic environment.

It should be noted that if the cerebellum was involved with manganese neurotoxicity causing cerebellar hypoperfusion, one would expect an underestimation of the reduc-

tion in cortical-to-cerebellar ratios. A relative decrease in perfusion of the cerebellum on the initial scan, followed by more normal cerebellar perfusion on the follow-up scan would result in lower caudate and thalamic-to-cerebellar ratios during the state of neurotoxicity, compared to the 9-mo follow-up scan.

Manganese poisoning occurs in three stages (*23,24*). The first stage exhibits psychiatric disturbances, including asthenia, anorexia, insomnia, hallucinations, mental excitement, aggressive behavior and incoherent talk (*2*). Increased neurological symptoms, including abnormal gait, expressionless facies, speech disorders, clumsiness and sleepiness, are seen in the second stage. The third stage includes progressive bradykinesia, asthenia, paresis, dysarthria, dystonia, impaired coordination and disturbances of gait (*24*). The patient in this report has developed Stages 1 and 2 chronic toxic encephalopathy, resulting in significant psychological and neurological impairments (*24,25*).

The patient's abnormal brain SPECT scan demonstrating decreased thalamic and right caudate head nucleus rCBF indicates that there was possibly a functional impairment of these structures. Decreased function of these structures, as seen here, has been shown to cause similar neurologic deficits in other patients (*7*). The abnormal rCBF brain SPECT contributed to her earlier diagnosis of probable toxic encephalopathy and the subsequent recommendation that she not return to the manufacturing plant. Since Stage 3 manganese intoxication had not yet fully developed, this patient was spared further damage by altering her work environment.

Nine months after her removal from the toxic environment, all follow-up toxicology and neurological examinations were normal. The follow-up rCBF brain SPECT scan showed normal rCBF to the initially decreased caudate head nuclei and both thalami. Our results emphasize the important role that rCBF brain SPECT scanning may serve in providing objective data to confirm early CNS damage from toxic exposure to environmental and/or industrial chemicals.

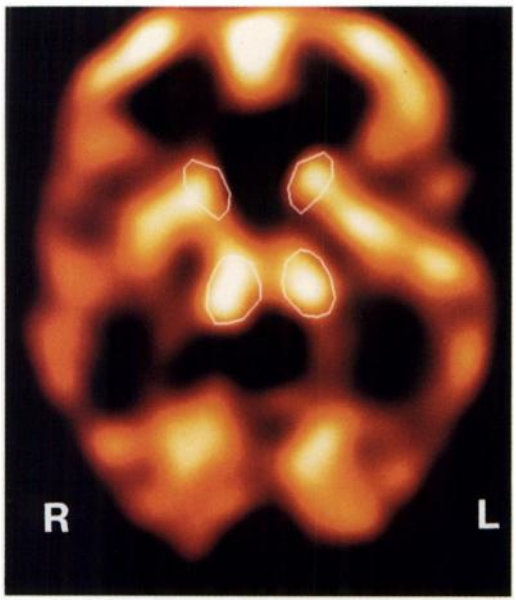

FIGURE 2. Brain SPECT scan image shows the ROIs used to obtain the rCBF activity of the caudate head nuclei and thalami for the initial and follow-up scans. The image was produced by summing three sequential rCBF brain SPECT scan sections (top row right, bottom row left, and bottom row middle) of the series of six images shown in Figure 3B.

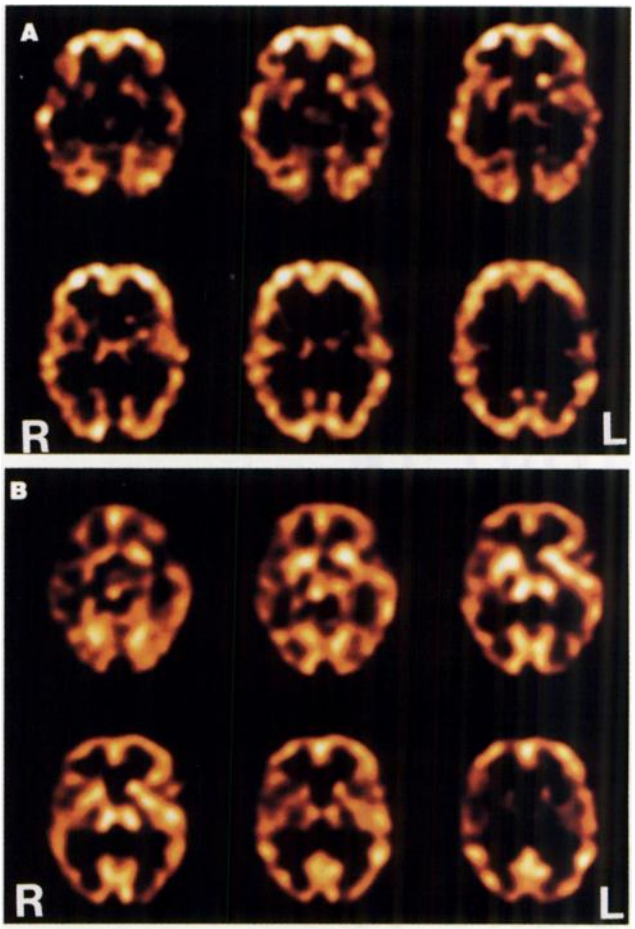

FIGURE 3. (A) Six serial sections through the level of the basal ganglia showing the marked diminution of rCBF to the caudate right nucleus and thalami. The six images (left to right, top to bottom) are contiguous sections 3.92 mm in thickness. (B) Six serial sections through the level of the basal ganglia show normal rCBF to the caudate nuclei and thalami. The six images (left to right, top to bottom) are contiguous sections 3.92 mm in thickness.

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