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Functional neuroimaging for clinical evaluation of mild-to-moderate toxic encephalopathic brain disease: A study of seven patients

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Abstract

Purpose. Numerous studies have found that exposures to neurotoxins such as solvents, pesticides, heavy metals, carbon monoxide and mycotoxins can cause many neuropsychiatric deficits. Neuropsychological test batteries are often useful in diagnosing and treating neurotoxin exposed patients; however, these batteries have a number of shortcomings. Increasingly, brain scans with SPECT (Single Photon Emission Computed Tomography) are being used to diagnose neurotoxin-exposed patients. The purpose of this study is to measure specific regional brain functional findings with SPECT on seven patients with various encephalopathic diseases and occupational and/or environmental chemical exposure.

Design. Case series.

Methods and materials. Detailed exposure/occupational histories were made of seven patients exposed to neurotoxins. Some patients had possible confounding factors such as a past history of alcohol abuse or mild trauma brain injury. SPECT scans were taken with a triple headed SPECT camera on patients injected with $^{99}$Tc-HMPAO and brain blood perfusion was analysed digitally by the Hermes BRASS system.

Results. A variety of significant hypoperfusion defects were seen in brain SPECT scans in six of these patients including frontal, parietal and cerebellar regions as well as thalamic hyperperfusion seen in six patients.

Conclusions. With additional research and analytical refinement, SPECT studies have the potential to become an important tool for the differential diagnosis and treatment of encephalopathic patients with toxic chemical exposure.

Key words: SPECT, neurotoxicity, neuroimaging, solvents

Introduction

A number of studies have documented that exposure to neurotoxins such as pesticides, solvents, heavy metals, carbon monoxide and mould can cause neuropsychiatric problems. Pesticide exposure has been linked to peripheral nerve problems, depression, confusion, anxiety and poorer scores on neuropsychiatric tests [1–5]. Studies of petrochemical exposed patients have found many neuropsychiatric problems including significant deficits in memory, learning, visuospatial and psychomotor speed as well as increased fatigue, depression, anxiety and behavioural changes [6–11]. Low-level lead exposure has been linked to lower childhood intelligence and may increase rates of antisocial behaviour including delinquency and murder [12–14]. Several reports have noted neuropsychiatric deficits in persons exposed to moderate levels of carbon monoxide [15,16]. Studies of patients exposed to high levels of indoor mould have reported a high incidence of problems such as poor concentration, depression, chronic fatigue, confusion and lower scores on neuropsychiatric test batteries [17–19].

It is often difficult to accurately diagnose mild-to-moderate neuropsychological deficits from neurotoxin exposure. Neuropsychiatry test batteries have been useful for decades to diagnose neurological deficits [20–22]. However, the sensitivity of neuropsychiatric test batteries to detect mild toxic encephalopathy is only fair and analysis is often complicated by many other factors such as intelligence, education, age, general health, socioeconomic factors and gender [23,24]. Also, these test batteries are often not very useful in determining the anatomical location of the brain neurological deficits.

In recent years, such neuroimaging techniques as brain SPECT are being increasingly used to diagnose and document neurological deficits [25]. A moderate amount of information currently exists for using SPECT scans to assess neuropsychiatric disorders, such as mild traumatic brain injury and neurovascular, affective, psychotic and dementia disorders [26–33]. SPECT scans indicate frequent hypo- and hyperperfusion conditions in various parts of the brain of patients with various neuropsychiatric disorders.

For example, hypoperfusion deficits are common in patients following mild brain trauma and are especially prevalent in frontal, temporal, thalamus and basal ganglia areas [28,29]. Depressed patients often have hypoperfusion in frontal and temporal regions and hyperperfusion in the occipital and thalamic regions [31]. However, it is not known at present whether certain brain SPECT perfusion patterns are pathognomonic for specific neuropsychiatric problems.

A few published studies have employed SPECT scans in patients with exposure to petrochemicals, solvents, creosote, pesticides, heavy metals, acids, hydrogen fluoride, dioxins, carbon monoxide and mould [34–41]. The employment of SPECT has also been very useful in assessing brain deficits due to alcohol and drug abuse [42–45]; however, this report will focus on environmental exposures. Use of both neuropsychiatric test batteries and neuroimaging tests like SPECT and related technologies like PET (Positron Emission Tomography) and fMRI (Functional Magnetic Resonance Imaging) may be more sensitive and specific than test batteries alone and may be very helpful in the diagnosis, clinical management and disability documentation of neurotoxic diseases and other neuropsychiatric disorders. The colourful imagery of these scans makes them easier to understand for health professionals, patients and family members and for jurors in toxic exposure lawsuits.

This naturalistic study will examine the SPECT findings of seven consecutive patients with exposure to various neurotoxins including solvents, paints, gasoline, airplane fuel, cleaning chemicals, pesticides, perfumes, moulds and silicone breast implants. SPECT scans will be examined to see what perfusion abnormalities are found in the seven...
neurotoxin-exposed patients and/or whether or not they correlate types of neurotoxic exposures.

Methods

All SPECT scans were performed based on medical necessity in 2004. Detailed medical histories including lengthy interviewing for environmental and occupational exposures were conducted on all patients. All subjects reported significant exposure to toxins. Some of the patients also had other exposures that can cause encephalopathic injury, such as mild closed head injuries or past histories of alcohol/drug abuse. A consent form was signed by all patients.

SPECT scans were performed similar to the method of Pavel et al. [46]. Patients were injected with $^{99}$Tc-HMPAO (Technetium$^{99}$m hexamethylpropyleneamine) in doses adjusted to patient weight (15–30 mci). SPECT scan was performed with a triple headed gamma camera with ultra high resolution fan beam collimators. Data processing is based on reconstruction, filtering and reorientation, leading to three standard orthogonal cuts based on the longest anterior–posterior brain axis. A fourth axial display is also obtained along the temporal axis. The slices are displayed with a threshold of 40% and a discrete colour code of 21 shades. Multiple threshold volume displays at 55, 65, 85 and 90%, respectively, were obtained. In addition, each study is processed via an automatic Neurostat algorithm [47], which displays eight surface views, after normalization to the Talairach space.

The images were processed post-acquisition using HERMES software from Hermes Medical Solutions, www.hermesmedical.com. We normalized the images intensity and spatially co-registered them to the standard atlas. Forty-six regions of interest defined by HERMES software were evaluated for hyperperfusion and hypoperfusion. The statistical evaluation was obtained by means of Hermes BRASS (Brain Registration Analysis Software Suite) software comparing the patient to the Hermes normative database using a total count adjustment. The abnormality threshold was set to 2.5 mm with a standard deviation of 2.0.

Results

A summary of the patient’s demographics, exposures, health conditions and brain SPECT perfusion results is presented in Table I. All patients were of Caucasian descent. Figure 1 shows SPECT scan images of the areas of maximum hyperperfusion and maximum hypoperfusion in the seven patients.

Discussion

One or more areas of significant hypoperfusion were seen in six of the seven patients. Significant hypoperfusion was seen in five patients in the left or bilateral parietal lobule regions, three patients in the left or bilateral sensiomotor cortex, two patients in the left cerebellar white matter and two patients had significant hypoperfusion in the left or bilateral frontal cortex (see Table I).

Our findings of frequent brain hypoperfusion are consistent with other studies, which noted that patients exposed to solvents, carbon monoxide, pesticides and other neurotoxic chemicals frequently have brain hypoperfusion, especially in the frontal, parietal and
Table I. Summary of patient characteristics, health conditions and significant SPECT perfusion abnormalities.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Exposures and time frame of exposure</th>
<th>Health conditions</th>
<th>SPECT results</th>
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<td></td>
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<td>Significant hyperperfusion areas</td>
</tr>
<tr>
<td>1-AS</td>
<td>41</td>
<td>M</td>
<td>Paints, solvents, roofing sealant for ~20 years. Past history of mild closed head injury (age 10) &amp; moderate drinking for 20 years</td>
<td>Problems with memory, concentration and executive function. Depression</td>
<td>Left Thalamus*</td>
</tr>
<tr>
<td>2- BA</td>
<td>39</td>
<td>M</td>
<td>Airplane fuel and gasoline— including exposure in underground storage areas. Exposure for about past 20 years. Past history of moderate alcohol use</td>
<td>Major depression, sleep apnea, chronic fatigue, obsessive compulsive, impulse control problems, progressive executive function problems.</td>
<td>Left Thalamus**</td>
</tr>
<tr>
<td>3- FK</td>
<td>35</td>
<td>F</td>
<td>Cosmetics—about 12 years as cosmetician</td>
<td>Depression, affective dysregulation, multiple executive, concentration and memory deficits. Bilateral cholesteatomas with erosion into dura. Chronic fatigue. Multiple allergies and environmental sensitivities.</td>
<td>Left Thalamus*</td>
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<tr>
<td>4- LS</td>
<td>50</td>
<td>F</td>
<td>Mould infested home from 2000–2002</td>
<td>Memory loss, spatial function impairment, executive function impairment and chronic fatigue.</td>
<td>Left Thalamus*</td>
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<tr>
<td>5- DS</td>
<td>13</td>
<td>M</td>
<td>Mould infested home from 2000–2002</td>
<td>Chronic fatigue, memory loss, executive function difficulties—significant drop in school performance.</td>
<td>Right Parietal Temporal Cortex*</td>
</tr>
<tr>
<td>6-WM</td>
<td>46</td>
<td>F</td>
<td>Silicone breast implants for 12 years 1979–1991. Implants ruptured and leaked and had to be removed</td>
<td>Chronic fatigue, memory problems, migraine headaches, nausea, malaise. Executive function deficits.</td>
<td>Left Thalamus*</td>
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Statistical significance * p<0.05 (two tailed), p<0.025 (one tailed), ** p<0.01 (two tailed), p<0.005 (one tailed), *** p<0.001 (two tailed), p<0.0005 (one tailed).
temporal regions [34,37,38,40,48]. SPECT studies with chronic fatigue syndrome (CFS) and fibromyalgia patients have found significantly more areas of brain hypoperfusion as compared with controls, especially in the frontal and temporal lobes [49–51].

Depressed patients have been found to have significant hypoperfusion in the bilateral prefrontal cortex [52–54], the bilateral inferior frontal cortex [55] and in the bilateral occipital, left superior temporal and right parietal regions of depressed patients [56].

A Turkish study reported that 12 depressed patients with psychotic features had significant hyperperfusion to the left parietal cortex and left cerebellum as compared to 16 depressed patients without psychotic features \( (p<0.001\) for both comparisons) [53]. In our series, marked left parietal hypoperfusion was seen in four of seven patients (57%),
including several patients with major depression coupled with obsessive thoughts, impulse control difficulties and executive function problems.

Significant thalamic hyperperfusion was seen in six of seven patients (86%) in our series. Other studies have noted that thalamic hyperperfusion is common in patients with depression and CFS [57], while another study reported no significant differences in thalamic hyperperfusion in depressed vs non-depressed patients [53]. A Netherlands study of 15 patients with obsessive-compulsive disorder (OCD) found that seven had OCD symptoms significantly reduced with 12 weeks of fluvoxamine treatment [58]. All seven of these responding patients had significant hyperperfusion to the right thalamus and cerebellum [58].

One limitation to this study was that sequential scans over periods of time were not performed on the patients. Sequential SPECT scans over a several month period can be a good way to follow clinical progress over time. More study on sequential brain SPECT scans over a period of time is needed in order to help evaluate patient recovery from neurotoxic exposure and to evaluate response of neurotoxin-exposed patients to environmental, nutritional and pharmacological interventions.

Another limitation of this study is that some of the patients also had co-morbid factors for possible brain injury. Four of the patients in this study had toxic exposure without any other obvious encephalopathic exposures, while three other patients had toxic exposure coupled with mild closed head trauma, alcohol abuse or cholesterolomas with erosion into dura. In the future, SPECT studies may be very useful in determining and differentiating the encephalopathic effects of environmental toxins, drug/alcohol abuse, closed head trauma, infections, tumours and other factors.

Current SPECT studies, including this one, are limited by the current dearth of information on what constitutes normal brain SPECT scans. Such normal brain SPECT atlases may be very useful in precisely differentiating between normal and abnormal brain blood flows. Recently, a computerized SPECT brain analysis was constructed by using scans from 21 normal patients [59]. Others researchers have used SPECT to construct maps of age-related brain structural and blood flow changes [60].

**Conclusions**

Assessment of metabolic injury to various areas of the brain after toxic exposure to a variety of substances is essential for the development of a rational treatment initiative for the clinical management of the resulting toxic encephalopathies and their sequelae. The diagnostic exam for the evaluation of toxic exposure-related neurological damage is well established. However, the nuclear medicine brain SPECT scan (which provides a real time assessment of regional cortical and sub-cortical metabolic activity) is not yet considered an integral part of the basic diagnostic exam. We report here on a series from a neuropsychiatric medical practice (PE), in which brain SPECT demonstrates a number of clinical findings that contributed significantly to the development of rational treatment and clinical management strategies. We conclude that the use of brain SPECT should be considered an integral component of the comprehensive diagnostic evaluation of toxic exposure induced neurologic disorder and brain disease. More studies are necessary to address questions of characteristic findings with specific exposures, age, gender and ethnic variations, genetic vulnerability risk factors, treatment response and disease progression monitoring and the differential and complementary use of other functional neuroimaging techniques such as PET and fMRI.
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References


