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Neuropsychological Assessment for Detecting Adverse Effects of Volatile Organic Compounds on the Central Nervous System

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Because there are no direct biological markers for the substances implicated in indoor air exposure, it is impossible to directly measure if an individual or group of individuals has been exposed to a potentially neurotoxic substance in the workplace. Behavioral changes may be the earliest and only manifestation of central nervous system (CNS) effects and are often too subtle to be revealed by routine physical or neurological examination. Neuropsychological techniques are sensitive to subtle behavioral/cognitive changes that can result from exposure to neurotoxins. These techniques consist of oral and written tests that are administered by a trained examiner on a one-to-one basis. In general, a wide variety of cognitive domains are evaluated. The typical battery generally includes assessing orientation, attention, intelligence, language, visual memory, verbal memory, perception, visuoconstruction, simple motor speed, psychomotor speed, and mood. As with most assessment techniques, the neuropsychological methods have limitations. One major drawback is the availability of appropriate norms that are used to compare the results of a specific individual. Because these tasks are greatly affected by age, intelligence, and in some instances sex, the availability of appropriate norms is mandatory to determine if the CNS has been effected.

Although neuropsychological tests are sensitive to the presence of CNS involvement, they are not specific. Patterns of performance seen with specific instances of neurotoxic exposure may also be seen with a number of other diseases of the CNS such as dementia, cerebrovascular disease, hydrocephalus, or normal aging. In addition, neuropsychiatric symptoms such as anxiety and/or depression are often manifested as cognitive difficulties that will mimic the cognitive dysfunction seen with toxicity of the CNS. Some of the more sensitive neuropsychological tests are presented. Interpretations of test performance as they relate to toxic effects on the CNS are discussed.

Introduction

Substances that have been reported to cause changes in mood and behavior with low-level exposure include lead, mercury, *manganese, carbon disulfide, methylbromide, pentaborane,* ethylene glycol monoethyl ether, and narcotic solvents (*1*). The patient may complain of vague central nervous system (CNS) symptoms before any clear-cut CNS changes can be measured. In patients with known neurotoxic exposures, clinical complaints include inability to concentrate, loss of memory, depressed mood, anxiety, restlessness, loss of interest in work, changes in libido, general apathy, confusion, sleep disturbance ranging from insomnia to somnambulism, irritability, headaches, and weakness.

Unfortunately, biological markers for solvents that compose volatile organic compounds (VOC) in indoor air are difficult to measure because of their rapid metabolism and clearance. Because solvents are known to cause behavioral changes as a result of adverse effects on the nervous system, it has also been speculated that VOCs have a negative effect on the CNS. Because these behavioral changes are often too subtle to be revealed by routine physical or neurological examination, the measurement of cognitive ability using neuropsychological techniques provides a method, albeit indirect, for evaluating the integrity of the CNS.

Neuropsychological Effects

Abnormal neuropsychological results reflect CNS involvement. If CNS dysfunction exists, specific patterns of performance provide additional information about the nature of brain injury. These performance patterns will show if neuropathology is static or progressive, acute or chronic, diffuse or localized. If performance deteriorates after the individual is removed from the source of exposure, this indicates a progressive disease process that is uncharacteristic of solvent/VOC exposure. When results show a decline in a specific cognitive domain such as memory, which is inconsistent with the individual's general level of intelligence as determined by either test results, school records, or occupational achievement, then an acute process is likely and would be consistent with neurotoxic effects. Specific patterns of performance are examined to determine if brain injury is diffuse or localized. If findings are localizable, then a diagnosis of neurotoxic exposure to solvents/VOCs is unlikely and an EEG and CT/MRI are indicated.

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Neuropsychological Techniques

Historically, neuropsychological techniques have consisted of oral and written tests that are administered by a trained examiner on a one-to-one basis. Recently, a number of computerized test batteries have also been developed [i.e., the World Health Organization Neurobehavioral Test Battery and the Neurobehavioral Evaluation System-NES-2 (*2*)]. Advantages and disadvantages exist for both interviewer-administered and computer-administered tests. For interviewer-administered tests, the advantages include human interaction and encouragement by the examiner, the ability to determine problem-solving strategies by actually observing the individual perform the tests, and the ability to administer tasks requiring verbal presentation and verbal responses. For example, verbal memory cannot be adequately assessed by a computer without sophisticated computer hardware. The disadvantages of interviewer-administered tests include standardization of administration between different testers and between testing sessions. In epidemiological investigations, interviewer-administered tests are more labor intensive and require a large study team to administer the tests.

Computerized testing offers excellent standardization in administering and scoring these tests. Furthermore, in epidemiological studies, multiple work stations and computers can be set up to test groups of workers simultaneously. However, normative populations are not available for computer-administered tests, which is not the case for interviewer-administered tests. The normative values for interviewer-administered tests cannot be used to compare the results of written tests adapted for the computer because the performance demands of the tasks change even though the tests appear to be similar.

The cognitive domains, which are generally evaluated in any neuropsychological evaluation, are presented in Table 1. There are many well-standardized neuropsychological tests that can evaluate each of these cognitive domains. Lezak (*3*) describes most of the available tests and is an excellent reference source. The tests that will now be described have been chosen because they have proven to be useful in evaluating neurotoxic effects.

Orientation is generally evaluated by asking about person, place, and time or by a brief mental status examination such as the Mini-Mental State Exam (MMSE) (*4*). The MMSE was designed to detect dementia and delirium. Because the MMSE fails to detect impairment in approximately 50% of cases with either right hemisphere or diffuse brain damage (*5*), symptoms associated with neurotoxic exposure are often too subtle and too diffuse to be detected by this instrument.

Verbal Intelligence Assessment

Verbal intelligence can be assessed using the Verbal Subtests from the Wechsler Adult Intelligence Scales (WAIS-R) (*6*). For brevity of testing, the vocabulary subtest can be used alone to obtain a good estimate of verbal intelligence because it correlates ($r = 0.82$) with the full-scale intelligence score (*6*). On this test, definitions of vocabulary words presented orally by the examiner are required. The responses are scored by strict criteria. The time of administration is approximately 10 min. Performance on this test is very resistant to any CNS injury. Even in cases of probable senile dementia of the Alzheimer's type, performance is generally congruent with the person's premorbid level of intellectual functioning. In addition, this test is a better estimation of intelligence than level of education (*7*). In past eras, higher levels of education were the exception, rather than the rule, especially in women. Because verbal intelligence will affect performance on the majority of neuropsychological tests, it is necessary to predict the level at which someone is expected to perform. When performance in a specific cognitive domain (memory, for example) falls below level of intelligence, then a cognitive decline from baseline is indicated. When exposed versus unexposed groups are equated for intelligence in epidemiologic investigations, the vocabulary test has proven to be an excellent tool to measure general level of intelligence without having to administer an entire WAIS-R, which can require 1 to 1.5 hr to administer.

Table 1. Cognitive domains assessed

Orientation
Verbal intelligence
Language
Remote
Memory
Anterograde memory
Verbal
Visual
Visuoperception/visuoconstruction
Executive/motor
Depression/anxiety

Another test that correlates highly with the vocabulary test ($r = 0.74$) and is also resistent to CNS impairment is the similarities test from the WAIS-R (*6*). As the name implies, the formulation and expression of the similarity between objects and/or concepts such as the relationship between an orange and a banana is required.

Although there are many standardized tests to evaluate language and aphasia, such as the Western Aphasia Battery (*8*) and the Boston Diagnostic Aphasia Battery (*9*), extensive evaluation of this cognitive domain in suspected cases of neurotoxic exposure is unnecessary because most neurotoxins do not selectively impair language. However, if deficits in language are found (i.e., paraphasias), then an alternative etiology for symptoms is suggested. The significant aspects of language can be quickly assessed by confrontational naming, repetition of words and phrases, spontaneous writing of a sentence, writing a sentence to dictation, and rating verbal expression.

At low levels, neurotoxins affect new learning and recent memory, and they do not affect remote memory. If gaps exist in the individual's early memories, then a neurotoxic etiology is unlikely. Remote memory can be assessed by asking about significant early life events (wedding or occupational details, etc.).

Difficulties with anterograde memory (ability to learn new information) is one of the characteristics of neurotoxic exposure. Therefore, it is important to evaluate this cognitive domain thoroughly. The Rey Auditory Verbal Learning Test (RAVLT) (*10*) requires memorization of a list of 15 words that is presented orally by the tester. Since the entire list of words is administered a total of five times, measurements of immediate memory (performance on the first trial) and the ability to benefit from repetition of material or total recall (performance on trial 5) are provided.