ENVIRONMENTAL NEUROLOGY:
CLINICAL NEUROLOGIC ASPECTS OF ENVIRONMENTAL TOXICITY

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New Trends in Environmental Injury

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NEUROTOXICITY ASSESSMENT

GENERAL TOXICITY

Biological toxicity denotes the ability of a chemical or compound to exert damage on a biological system. The most common routes of exposure in human toxicity include inhalation, dermal and ingestion. Due to the volatile nature of most neurotoxin, the most common route of exposure is inhalation. However, deliberate ingestion and accidental immersion in toxins are also known to result in neurologic damage.[1] After inhalation, solvents are rapidly absorbed into the blood stream.

Many neurotoxin are highly lipophilic, meaning they demonstrate a natural affinity to bind to lipids (fatty tissues). Neurotoxin tend to accumulate in the fatty tissues of animals. It is for this reason that the use of **adipose tissue biopsy and pathologic examination** can be a useful indicator of toxic exposure.

The high solubility of solvents in lipids combined with the high lipid content of the nervous system creates a medium for significant morbidity and potential mortality. The central nervous system (brain and spinal cord) and the peripheral nervous system (peripheral nerves, sensory and motor nerves) are composed in a large part by lipid tissues. Toxins will therefore accumulate in the nervous system. This lipophilic tendency of toxins is bolstered by the rich blood supply to the brain by the circulatory system, which can lead to serious neurological effects.

OVERVIEW OF SYMPTOMS

Neurologic symptoms of toxic exposure are specific to the particular neurotoxin. Solvents, one of the most prevalent nervous system toxins, may induce euphoria followed by confusion, tinnitus, disorientation, blurred vision, analgesia, headache, nystagmus and ataxia. Neurobehavioral problems from solvent exposure include memory loss, decreased attention, altered personality or mood, reduced psychomotor

functioning, impaired dexterity and hand-eye coordination, altered reaction time and decreased problem solving ability.

DIAGNOSTIC EVALUATION

There are four essential elements to diagnosing neurologic injury with toxic exposure etiology

1. Identification of the precipitating event for the onset of symptoms, for example, a spill.
2. Generation of a hypothesis regarding the relationship of the precipitating event and the subsequent symptoms.
3. Diagnosis must include a description of the precipitating event, optimally with quantification utilizing industrial hygiene data or other natural factors.
4. The diagnosis must include the clinical assessment of the suspected association between exposure and organ or system dysfunction in the patient.

MEDICAL/NEUROLOGIC EXAMINATION

Questionnaire. A comprehensive questionnaire should be given to the patient[2] and the patient should be asked about personal habits, hobbies and occupational duties for evaluation of potential exposures. Past medical history should be obtained for consideration of the potential for underlying systemic disease or prior neurologic injuries. The history should also consider socioeconomic factors and potential nutritional deficiencies that may have neurologic implications. The occupational history should be explored for timing of symptoms relative to work exposure and whether symptoms or illness have occurred in coworkers. A description of all job titles and type of work performed is helpful, and should be obtained whenever possible.

History. A complete history should be taken as soon as possible after neurotoxic exposure occurs or is suspected to have occurred. The history should include medical, personal and occupational information. It should include data on symptomatology, particularly observable abnormalities such as tremor, convulsions, vertigo, seizure history, and weakness. It is important to document the main complaint and the onset of the present illness.

Medication History. All former and current prescribed and over the counter medications should be evaluated. Toxic dementias can be associated with or caused by a large number of legally prescribed medications. Antipsychotics, hypnotics, sedatives, anticonvulsant, anticholinergic, and various pain relievers can produce encephalopathy. Higher cortical functioning may be impaired, altered, or diminished by benzodiazepine use. Chronic use of anticonvulsants will cause subtle central nervous system effects.

Personal, Avocational and Social History. Personal history should include an investigation of the patient's living environment and careful screening for illegal drug use. Occult exposure to carbon monoxide will result in headache and nausea, and drugs such as opiates will also lead to neurotoxic effects. Hobbies such as modeling, gardening or painting can also expose the individual to known neurotoxins. The careful examination must include questions examining these potential sources of toxic exposure.

Physical Examination. A complete physical examination and neurologic examination should be conducted. Vital signs, weight, blood pressure should be recorded. The head, neck, eyes, nose and throat should be examined. Special attention should be paid to the skin, lymph nodes, and liver and spleen. The neurologic examination should evaluate higher cortical functioning as well as brain stem functions. Examination of higher intellectual functions includes determining orientation to time,

place and person. The neurologic examination should evaluate memory, apraxia, agnosia (visual, auditory and tactile), aphasia, cranial nerves, visual acuity, motor systems, reflexes, sensory systems, and cerebellar functioning (posture, gait, ataxia). Clinicians should also assess the patient's overall mental and behavioral state.

Laboratory Diagnostic Procedures.

Routine Blood Work. Routine blood work should include a complete blood chemistry profile and urinalysis. There are also some specific analytic tests for particular neurotoxins that the clinician may suspect are involved, including screening for metabolites of solvents in blood or urine. **Liver function** tests can indicate if this organ is being stressed by efforts to remove toxins from the circulatory system.

Structural Imaging. A multitude of diagnostic techniques are available to evaluate structurally and functionally the central, peripheral and autonomic nervous systems. The need for structural evaluation of the brain may be indicated in some patients. Structural imaging can be accomplished with computed tomography (CT or CAT), magnetic resonance imaging (MRI), or positron emission tomography (PET). Chronic exposure to solvents is known to result in cerebral atrophy which can be demonstrated on CT scanning.

Electrophysiologic Examination. Functioning of the central and peripheral nervous systems can be evaluated by electromyography (EMG), nerve conduction velocity testing, electronystagmography (ENG), audiologic testing, and balance evaluation. The autonomic nervous system can evaluated by pupillometry, electrocardiographic R-R peak interval, and sweating evaluation.

Electroencephalographic Examination. I have previously published a treatise on the clinical evaluation of patients exposed to neurotoxicants.[2] In

this work I address the fundamentals of diagnosing neurotoxic illness. A multitude of diagnostic techniques are available to evaluate structurally and functionally the central, peripheral and autonomic nervous systems. The need for structural evaluation of the brain may be indicated in some patients. Structural imaging can be accomplished with computed tomography, magnetic resonance imaging, or positron emission tomography. Functioning of the central and peripheral nervous systems can be evaluated by electromyography, nerve conduction velocity testing, electronystagmography, audiologic testing, and balance evaluation. The autonomic nervous system can evaluated by pupillometry, electrocardiographic R-R peak interval, and sweating evaluation. Neurometric techniques can be quantitative or semi-quantitative. An electroencephalogram provides classic recording of the brain electric activity, and is discussed in greater detail below. Evoked potentials or evoked responses can be recorded using visual, auditory, somatosensory, cognitive, or brain stem stimulation. Semi-quantitative sensory evaluation measures current perception threshold, vibratory perception threshold and thermal perception threshold.

Electroencephalograms are a functional measurement of the brain's electrical activity. Electroencephalograms are different from traditional magnetic resonance images or computed tomographic images of the brain in that the latter provide morphological information, structural or anatomic details, whereas the former provide information concerning the functional electrical activity of the brain. Computed tomography of a dead person may be viewed as "normal", however the electroencephalogram would be highly abnormal. Electrodes placed in specific positions record the brain's electrical activity, and plot this information in wave form on polygraph paper. These polygraphs are read or interpreted by physicians with specialty training, and can offer valuable information regarding potential organicity of neurologic or

psychiatric complaints of subjects.

Quantitative electroencephalography, which has also been known as Brain Electrical Activity Mapping, EEG Brain Mapping, or EEG topography, involves electroencephalographic frequency analysis, topographic display, and statistical comparisons to a normative database of data received from evaluating a population considered "normal" in all aspects and which are age and sex matched to the individual being examined. ~~The clinical usefulness of the quantified electroencephalogram is limited.~~

QEEG →

There are early animal studies that have reported excessive beta activity in the brains of monkeys and humans following toxic exposure on the quantitative electroencephalogram.[3, 4] A study published in June of 1992 in the journal "Electroencephalographic and Clinical Neurophysiology" by Dr. Jonkman and associates of the Westeinde Hospital, The Hague, The Netherlands. Dr. Jonkman and associates studied the quantified electroencephalograms of workers occupationally exposed to known solvents and organophosphorus pesticides. Among their findings, Dr. Jonkman reported increased beta activity when compared to normal controls.[5] Electroencephalographic studies have been used for the detection of subtle toxic agent-induced dysfunction, and are an integral part of the Russian and European neurotoxicological studies.[6]

Case Study: Solvents

ACUTE AND CHRONIC EFFECTS OF SOLVENT EXPOSURE

Acute effects of exposure to organic solvents consist of feelings of dizziness, lightheadedness and incoordination, and possibility short-term psychomotor impairment. Removal of the patient from the source of exposure is reported to result in total resolution of symptoms.

Chronic neurological and neuropsychological effects of solvent exposure symptoms include increased fatigue, irritability, depression and loss of interest in daily activities. There have also been reports of cerebral atrophy, deficits in learning and memory, reduction in psychomotor and short-term memory ability. As the severity of CNS dysfunction increases, the likelihood of a reversal of symptoms becomes progressively less likely.[7] The peripheral nervous system may show peripheral neuropathy, which can be examined histologically or through electrophysiologic techniques.

Swedish workers diagnosed with solvent induced toxic encephalopathy have been known to demonstrate central nervous system effects up to five years after cessation of exposure on psychometric evaluation. The most common symptoms among these workers were memory disturbances, difficulty in concentration, fatigue, lack of initiative, and mood effects such as irritation and depression.[8] A separate epidemiologic study comprising 295 men aged 57 to 75 years who had been exposed to mixed solvents over a period of 5 years or more demonstrated significantly more complaints than controls of decreased concentration ability and memory difficulties, and of headache in those workers that had retired. It is important to note that this study was controlled for over-reporting of symptoms.[9]

Biological Markers. Surveillance of employees exposed to solvents might require measurements of chemical products in body fluids, usually blood or urine, occasionally breath. Timing of sample collection is essential to this determination. Biological markers are defined by the National Research Council as the measure of change or variations in biological systems or samples. A change may occur at the molecular level as a sign of exposure to a chemical with no clinical significance. For example, delta-aminolevulinate dehydratase enzyme inhibition is a marker for lead exposure with no known deleterious effects.

Markers for effects can indicate potential or existing disease; for example changes in organ function. In this case, certain laboratory tests of organ functions may be altered as a result of disease caused by the exposure. Routine function tests, however are not as a rule sensitive or specific to be of value in the detection of early pathology.

The phrase "Risk Assessment" usually involves estimates of risks to humans extrapolated from high-level experimental doses used in animal tests. Most tests have been performed with the primary objective of assessing carcinogenicity of chemicals, and cancer is used as an end point. The paradigms commonly used for the detection of cancer do not adequately apply to neurotoxins. Most hazards assessed in terms of solvent exposures are considered qualitative rather than quantitative in nature.

Screening and surveillance of workers should include a careful occupational and social history, hobbies, and use of cosmetics, detergents and other household items, as well.

DIFFERENTIAL DIAGNOSIS OF NEUROTOXIC EXPOSURE

The clinician must rule out other conditions that may mimic the symptoms of toxic exposure. The clinician must be aware of systemic conditions or aspects of the patient's medical history that may produce symptoms similar to solvent induced toxic encephalopathy. For example, Multiple Sclerosis (MS) and Systemic Lupus Erythematosus (SLE) can produce the central nervous system and peripheral system findings typical of solvent exposure. However, conditions such as these can be ruled out with hematologic, immunologic, or imaging studies such as CT or MRI. These techniques can also rule out infection or tumors that may be the cause of symptoms. A history of head injury should be carefully evaluated, as many patients suffering from post-concussive syndrome may exhibit electroencephalographic and neuropsychologic results which are indicative of organic solvent exposure. Additionally, any history of excessive alcohol intake should be carefully investigated. A personal or family history of psychiatric disease should be excluded as an etiologic factors in the patient's current symptomatology, as should vitamin or nutritional deficiencies, such as B12 deficiency, which can produce neuropathic or psychotic symptoms.

References

1. Tsuruta H. Percutaneous absorption of organic solvents: Comparative study of the in vitro percutaneous absorption of chlorinated solvents in mice. Industrial Health. 1975;13:227-236.

2. Bernad PG, Saunders GS. Evaluation of patients exposed to neurotoxicants. Clinical Toxicology I. Clinics in Laboratory Medicine. 1990:10(2);387-402.

3. Duffy FH, Burchfiel JL, Bartels PH, Gaon M, Sim VM. Long-term effects of an organophosphate upon the human electroencephalogram. Toxicology and Applied Pharmacology 1979 Jan;47(1):161-76.

4. Burchfiel JL, Duffy FH, Van Sim M. Persistent effects of sarin and dieldrin upon the primate electroencephalogram. Toxicology and Applied Pharmacology 1976 Feb;35(2):365-79.

5. Jonkman EJ, et al. Electroencephalographic studies in workers exposed to solvents or pesticides. Electroencephalography and clinical Neurophysiology. 1992;82:438-444.

6. Horvath M, Frantik E. Quantitative interpretation of experimental toxicological data: the use of reference substances. In: Horvath M, ed. Adverse effects of environmental chemicals and psychotropic drugs. New York, Elsevier, 1973. Vol. 1, pp. 11-21, and Horvath M, Frantik E., ed. Adverse effects of environmental chemicals and psychotropic drugs: neurophysiological and behavioral tests. New York, Elsevier, 1976. Vol 2, 334 pp. as per Environmental Health Criteria 60: Principles and methods for the assessment of neurotoxicity associated with exposure to chemicals. World Health Organization, Geneva 1986, pp. 63.

7. Baker and Fine, JOM 28(2):1986.

8. Edling C, et al. Long Term Follow up of workers exposed to solvents. British Journal of Industrial Medicine. 1990; 47:75-82.

9. Hein HO, Suadicani P, Gyntelberg F. Mixed solvent exposure and cerebral symptoms among active and retired workers. An epidemiologic investigation of 3387 men aged 53-75 years. Acta Neurol Scand. 1990 Feb;81(2):97-102.