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news

Pathology Perspective

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Alzheimer's Disease -A New Look At An Old Protein

By: Robert Rosecrans, Ph.D. Clinical Director of Glenbrook and Highland Park Hospitals, Director of Point of Care Testing

For over 100 years since Alois Alzheimer described the disease that bears his name, the medical community has been frustrated by the lack of advancement in treatment. As life expectancy has increased over the last century from 48 years of age to those born in 1900 to 78 years of age to those born in 2004, virtually every family has or will be affected by Alzheimer's Disease (AD).

β-Amyloid, the instigator of the nerve cell death in AD, is involved in plaque formation and has been the focus of drug therapy for the last 20 years (1). Scientists have known that β-amyloid and the protein tau are both prevalent in the brains of AD patients. β-amyloid is found in the plaque which is found outside dead and dying nerve cells. Tau is found inside the nerve cell in the mesh of proteins known as the neurofibrillary tangles. Normal tau protein binds to the microtubles in the axon stabilizing the structure and providing a transport system for nutrients. Researchers looked at both β-amyloid and tau as targets for understanding and providing a pathway for some therapeutic intervention in the disease. 16 years ago a mutation in the *APP* gene, which provides the amyloid precursor protein for β-amyloid, was discovered in patients with hereditary AD. Since the discovery, research has focused on β-amyloid in the hope of supplying answers to the disease pathogenesis but has met with limited success. Tau took a backseat in AD research for many years but this is changing.

Recent animal studies show tau may play a more prominent role in AD than previously suspected. Using genetically engineered mice having a mutant form of the human *APP* gene and a normal complement of tau, researchers found mice developed amyloid plaque but did not develop the neurofibrillary tangles or the neuronal loss (2). From these experiments it appears that mutations in the tau gene may be responsible for the downstream formation of the neuronal tangles and cell death. For reasons not understood tau becomes hyper-phosphorylated in AD and cascades into cell death.

Memantine one of the few drugs approved for treating AD has demonstrated limited success in clinical deterioration. Memantine was developed as a glutamate receptor antagonist, which acts by decreasing neuronal excitatory toxicity. Recent studies in cell cultures show that memantine also decreases tau phosphorylation and inhibits neurofibrillary degeneration.

Researchers are looking at the role of β-amyloid and now tau in the pathogenesis of AD. From the recent work on tau protein, it appears future treatment of AD patients will not only involve the reduction of plaque formation by β-amyloid but also the relationship of the tau protein to the formation and prevention of the neurofibrillary tangles.

Reference:

1. Roberson E., Mucke L, 100 Years and Counting: Prospects for Defeating Alzheimer's Disease *Science* 2006:341;781.
2. Roberson E., *et.al.*, Reducing Endogenous Tau Ameliorates Amyloid β-Induced Deficits in an Alzheimer's Disease Mouse Model *Science* 2007:316;750-58.

Mercury Toxicity Update

Mercury toxicity was described in a previous issue of Pathology Perspective in which a patient self administered the element by injection under the skin. Mercury is sold as "azogue" or quicksilver and used in some religious ceremonies where the mercury is spread around living spaces, worn in a pouched bag around one's neck, or burned in a candle, all done with the intent of "warding off evil spirits." Another group of people believe that injection of mercury under the skin will boost their immune system and prevent disease.

Secondary mercury contamination is problematic and caused when mercury is spread around living areas where it is absorbed into carpeting, floorboards, and walls. Unsuspecting individuals may be exposed to mercury vapor in apartments vacated by users. Infants and children are more prone to exposure as they crawl and play on the floor. Elemental mercury is readily vaporized and 80% of the vapor is absorbed across the aveoli. Inorganic mercury attaches to sulfhydryl groups and will affect protein functioning. One sulfhydryl functional change caused by mercury is to decrease the production of acetylcholine which leads to the characteristic motor dysfunction observed in toxicity.

The June 15, 2007 Morbidity and Mortality Weekly Report describes another potential source of mercury contamination by household products, specifically antiques. Vintage clocks, barometers, mirrors, and lamps may all contain mercury housed in a sealed container. Seals on antique products can crack with age and allow the mercury to leak and vaporize. If antiques are dropped, mercury will spread on the floor into those shiny, "fun" little silver balls and contaminate carpeting, floors, floorboards, etc. Vacuuming the mercury only worsens the situation as the household vacuum cleaner becomes contaminated. It is advisable that State Public Health Services be notified to insure proper decontamination of mercury.

Short term exposure to high levels of elemental mercury can cause lung damage, nausea, vomiting, diarrhea, increased blood pressure and heart rate, skin rashes, and eye irritation. Exposure to high levels of mercury vapor can permanently damage the brain, kidneys, and developing fetuses. Laboratory testing for mercury will confirm exposure but a new source of contamination may be linked to the inadvertent leakage or breakage from antique products.

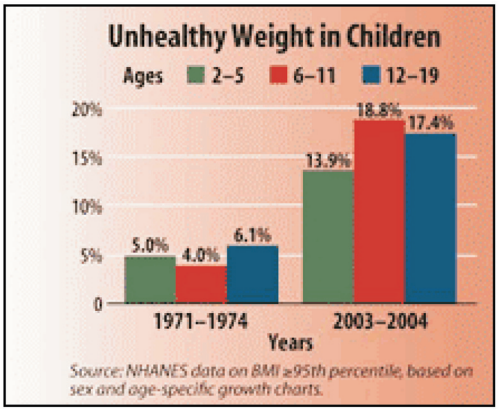
Reference

Elemental Mercury Releases Attributed to Antiques - New York, 2000-2006. *MMWR* 2007:56(23);576-79.

AHA Expands Lipid Screening for Overweight Kids

In March of 2007 the American Heart Association (AHA) published a statement in *Circulation* expanding the lipoprotein screening guidelines published in the 1992 consensus report by the National Cholesterol Education Program (NCEP) Expert Panel on Blood Cholesterol Levels in Children and Adolescents. The 1992 consensus report recommended two strategies for lowering cholesterol in the pediatric population. One strategy was based on a population approach and another based on targeted screening. The population based approach recommended that children >2 years of age adopt a fat and cholesterol restricted diet that had an appropriate caloric amount to maintain a desirable body weight. The target screening method recommended that children be screened for cholesterol levels if they had a family history of coronary heart disease. The target screening population being defined as having a parent or grandparent <55 years of age who has evidence of coronary heart disease, peripheral vascular disease, or cerebrovascular disease.

Since the NCEP guidelines were published several of the recommendations have been challenged. In 1992, the NCEP estimated that 25% of children and adolescents would be targeted for cholesterol screening based on a population based study, however, this number has been found to be low. Compounding the estimated data is the fact that the 1992 NCEP guidelines for cholesterol screening did not account for variability in cholesterol and HDL cholesterol based on race, gender, and sexual maturation. The latest population based study data demonstrates that between 36% and 46% of children and adolescents should be screened for cholesterol. The proposed population range varied depending on location with 36% of Utah high school students needing cholesterol screening to 46% of California students.



Since 1992 there has been a growing epidemic of childhood obesity and consequently the NCEP guidelines were not able to incorporate this unknown trend. The AHA recommends that overweight and obese children receive fasting lipid profiles and the patients be screened for other aspects of metabolic syndrome such as insulin resistance, type 2 diabetes, hypertension, and central adiposity. The AHA goes further in recommending that other risk factors be assessed in children for those at high coronary risk, namely smoking, cigarette smoke exposure, low HDL, high triglycerides, and possibly cardiac risk markers such as CRP. Effective life style changes must also be incorporated into the pediatric population to stem the trend toward obesity and high risk lipid abnormalities.

Reference

McCrindle B., et.al. Drug Therapy of High-Risk Abnormalities in Children and Adolescents. A Scientific Statement From the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, With the Council on Cardiovascular Nursing. *Circulation* published on line Mar 21, 2007; DOI:10.1161/CIRCULATIONAHA.107.181946.

Question & Answers

Response by: Robert Rosecrans, Ph.D., Clinical Director of Glenbrook and Highland Park Hospitals, Director of Point of Care Testing

Q. A 75 year old female was admitted to the Emergency Department from a nursing home with a diagnosis of being unresponsive. During the workup of the patient the ED physician ordered a drug of abuse screen. The laboratory reported the urine sample as positive for benzodiazepines, opiates, and THC. The ED questioned the positive result for THC as the patient's family vehemently denied the she was using marijuana. Two urine drug samples were sent to the laboratory at the same time from the ED, one from the 75 yr old patient and one from a teenager. To insure there was not an error in testing, the samples were repeated and the same results were obtained. The 75 yr old was admitted to the ICU and the laboratory recommended that a fresh sample be collected for drug of abuse testing. The second sample was tested and the same results were obtained: positive for benzodiazepines, opiates, and THC. The laboratory procedure is to confirm all positive drug of abuse testing unless the ordering physician cancels the confirmation. The urine sample collected in the ED and one collected in the ICU were sent to an outside laboratory

for confirmation by gas chromatography/mass spectrometry (GC/MS). Both samples confirmed the presence of benzodiazepines and opiates but THC was negative. The attending physician questioned what happened and how this occurred.

A. The laboratory uses an immunoassay method to screen urine samples for ten drugs of abuse. Immunoassays are based on the reaction of a drug metabolite and an antibody that is coupled to either a fluorescent signal or an enzyme reaction. The antibody reactions are prone to cross-reactivity with other compounds and can lead to a false positive result. Review of the patient medical record indicated that among the drugs she was taking hydrocodone accounted for the positive opiate screen and Ativan for the positive benzodiazepine screen. Other drugs being taken included: Protonix, antihistamines, and bronchodilators. Protonix is known to cross-react with the immunoassay reactions used for drug of abuse testing and cause a false positive reaction for marijuana. Review of the product insert for Protonix warns of this complication in laboratory testing for marijuana. Other drugs used to treat GERD that have the potential to cross react with the marijuana immunoassay include: Nexium, Prilisec, and Prevacid. Marinol, an analogue of THC that is FDA approved as an appetite stimulant, will cross react with the THC immunoassay causing a false positive test for marijuana. GCMS confirmation will discriminate the drugs noted above from the active marijuana compound, delta-9-tetrahydrocannabinol.

The laboratory confirms all positive drug screens by sending the specimens to a facility that will perform GCMS testing on the sample. GCMS is a laborious, time consuming, and an expensive procedure whereby samples must be extracted, derivatized, run through a chromatography column, and then run through a mass spectrometer. The advantage of GCMS is that it will physically separate the compounds thus avoiding the possible pitfall of a false positive reaction due to antibody affinity. GCMS is often referred to as the "gold standard" in drug confirmation testing, however, even this tool is not fool proof and will miss some compounds. Although it may be tempting to assume the drug screen is positive for a particular drug, it is essential to wait for the confirmatory testing. If there are any questions concerning drug of abuse testing or a discrepancy in the testing, please contact James Dohnal, Ph.D. at 847-570-2784, jdohnal@enh.org or Robert Rosecrans, Ph.D. at 847-926-5078, rrosecrans@enh.org

New Residents

The Department of Pathology and Laboratory Medicine welcomes the following physicians to its residency program:

Jennifer Bero, M.D., Medical College of Wisconsin.

Cynthia Kelley,M.D., Ross University, Portsmouth, Dominica

Bryan Schmitt, D.O., Des Moines University College of Osteopathic Medicine

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