Biomedical Update:

Loss of seizure control: check vitamin D levels

Kuwaiti researchers report that patients who undergo long-term treatment with anticonvulsant drugs can develop seizures due to drug-induced vitamin D deficiency.

F. E. Ali and colleagues describe one patient, a 32-year-old mentally retarded man, who began having seizures after five years of successful treatment with phenobarbital and phenytoin (Dilantin). Overall, the man had been treated with anticonvulsants for 20 years. Lab tests revealed vitamin D deficiency with associated calcium deficiency, and administration of vitamin D and calcium restored effective seizure control.

The researchers note, "Antiepileptic drugs cause vitamin D deficiency through induction of hepatic microsomal enzymes that metabolize vitamin D. Institutionalized subjects are more vulnerable because of the added factors of multidrug therapy, poor diet, reduced exposure to sunlight, and physical inactivity."

Ali et al. recommend that doctors check for vitamin D or calcium deficiency in patients experiencing a recurrence of seizures after long-term anticonvulsant therapy, and that institutionalized patients taking anticonvulsants be given vitamin D supplements.

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"Loss of seizure control due to anticonvulsant-induced hypocalcemia," F. E. Ali, M. A. Al-Bustan, W. A. Al-Busairi, and F. A. Al-Mulla, *Annals of Pharmacotherapy*, Vol. 38, No. 6, June 2004, 1002-5. Address: F. E. Ali, Medical Rehabilitation Center, P.O. Box 1240, Surra 45713, Kuwait, fawzi@kma.org.kw.

PDD: More evidence of environmental factors

A recent study adds to evidence linking autism to environmental factors present in industrialized societies.

Using data from a Social Security registry and the National Bureau of Statistics, Israeli researcher A. Kamer and colleagues identified 1,004 children diagnosed as having pervasive developmental disorder (PDD). The researchers divided the children into four groups: native Israelis of non-Ethiopian extraction, native Israelis of Ethiopian extraction, immigrants of non-Ethiopian extraction, and immigrants born in Ethiopia. This allowed the researchers to analyze differences between children born in Israel, a highly industrialized country, and Ethiopia, a developing country.

The researchers found that the rate of PDD was significantly lower in children who immigrated from Ethiopia than in children of Ethiopian extraction who were born in Israel. Also, the rate of PDD in Israeli-born children was higher than the rate of PDD in other immigrant children (who came from a mixture of industrialized and developing nations), while the Ethiopian-born children had lower rates of PDD than other immigrants.

Kamer et al. say their findings "may indicate that gestation, birth or infancy in industrialized countries exposes children to environmental insults that increase the risk for contracting PDD."

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"A prevalence estimate of pervasive developmental disorder among immigrants to Israel and Israeli natives—a file review study," A. Kamer, A. H. Zohar, R. Youngmann, G. W. Diamond, D. Inbar, and Y. Senecky, *Social Psychiatry and Psychiatric Epidemiology*, Vol. 39, No. 2, February 2004, 141-5. Address: A. Kamer, Psychology Behavioral Science, Ruppin Academic Center, 40250, Emek Hefer, Israel.

Vision study implicates cerebellar defects

A new study of visual anomalies in high-functioning autistic individuals supports previous findings implicating defects of the cerebellum in autism.

Yukari Takarae and colleagues investigated visually guided saccades in 46 autistic individuals and 104 age- and IQ-matched nondisabled controls. (Saccades are sudden, rapid eye movements that shift the direction of gaze from one point to another.) The researchers report that "individuals with autism had increased variability in saccade accuracy," and that autistic subjects without delayed language development displayed a mild saccadic hypometria ("undershooting" resulting in failure to reach a target).

The researchers conclude, "The observed saccadic abnormalities suggest a functional disturbance in the cerebellar vermis or its output through the fastigial nuclei," which is consistent with cerebellar defects reported by multiple MRI studies. The differences between subjects with and without delayed language development, they say, suggest that cerebellar pathology may vary in these groups.

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"Oculomotor abnormalities parallel cerebellar histopathology in autism," Y. Takarae, N. J. Minshew, B. Luna, and J. A. Sweeney, *Journal of Neurology, Neurosurgery, and Psychiatry*, Vol. 75, No. 9, Sept. 2004, 1359-61. Address: John Sweeney, Department of Psychiatry (MC 913), University of Illinois at Chicago, 912 S. Wood St., Suite 235, Chicago, IL 60612-7327, jsweeney@psych.uic.edu.

Controversy prompts call for registry of clinical drug trials

In the wake of the Food and Drug Administration's admission that antidepressants are dangerous and ineffective for pediatric patients (see page 2), a growing number of doctors are calling on the government to create a mandatory registry of clinical drug trials. The FDA's turnaround, these doctors point out, came only after researchers evaluated data from studies that initially were suppressed by drug manufacturers.

Overall, only about half of drug trials are ever reported. Those that do get published, physician Drummond Rennie notes in the *Journal of the American Medical Association* (*JAMA*), show "a persistent bias in favor of positive results and therefore in favor of the newer and more expensive treatments." Rennie, a deputy editor of *JAMA*, adds, "Another consequence is that harmful effects found in unpublished trials disappear without a trace, since the U.S. Food and Drug Administration has no mandate to report them to the public." By the time these adverse effects become public knowledge, Rennie notes, "direct and widespread harm" has already been done to patients.

Rennie notes that drug firms are now offering to set up voluntary trial registries, but he points out that a similar action by the Association of the British Pharmaceutical Industry resulted in poor compliance. Rennie and colleague Kay Dickersin are calling on the government to establish an adequately funded mandatory registry "of all trials in all conditions," so that data from both positive and negative studies will be available to researchers.

"The storm over SSRIs," Rennie says, "is a good demonstration that no clinician can possibly practice evidence-based medicine if prevented from seeing the evidence."

Voicing similar concerns, the International Committee of Medical Journal Editors recently announced that its members plan to begin refusing to publish papers on the results of any clinical trials that were not recorded in a publicly accessible registry at their outset.

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"Trial registration: a great idea switches from ignored to irresistible," Drummond Rennie, *Journal of the American Medical Association*, Vol. 292 (epub in advance of publication), September 2004. Address: Drummond Rennie, *Journal of the American Medical Association*, 515 N. State Street, Chicago, IL 60610.

—and—

"Medical journals to require clinical trial registration," *New Scientist*, September 9, 2004.