Research Briefs

A Faster Way to Diagnose Cushing's Syndrome

Diagnosing Cushing's syndrome can take 24 hours of complicated and repeated analysis of blood and urine, brain imaging, and tissue samples from sinuses. But that may soon be in the past: National Institutes of Health (NIH) researchers have found that measuring cortisol levels in hair samples can do the same job faster.

Patients with Cushing's syndrome have a high level of cortisol, perhaps from a tumor of the pituitary or adrenal glands, or as a side effect from medications. In the study, 36 participants—30 with Cushing's syndrome, six without—provided hair samples divided into three equal segments. The researchers found that the segments closest to the scalp had the most cortisol (96.6 ± 267.7 pg/mg for Cushing's syndrome patients versus 14.1 ± 9.2 pg/mg in control patients). Those segments' cortisol content correlated most closely with the majority of the initial biochemical tests, including in blood taken at night (when cortisol levels normally drop).

The study was small; Cushing's syndrome is rare, and it's hard to recruit large numbers of patients. Still, the researchers believe it is the largest of its kind to compare hair cortisol levels to diagnostic tests in Cushing's patients.

"Our results are encouraging," said Mihail Zilbermint, MD, the study's senior author and an endocrinologist at NIH's Eunice Kennedy Shriver National Institute of Child Health and Human Development. "We are hopeful that hair analysis may ultimately prove useful as a less-invasive screening test for Cushing's syndrome or in helping to confirm the diagnosis."

The authors suggest the test is also a convenient alternative with the "unique ability" for retrospective evaluation of hypercortisolemia over months.

Source: National Institutes of Health, February 2017

High Lead Levels From Old Bullet Fragments

Bullets and bullet fragments aren't always removed if they don't threaten the injured person's life. But years later, "retained" bullet fragments (RBFs) can lead to nonspecific symptoms of lead toxicity, such as fatigue, abdominal pain, and memory loss.

Routine testing of adults with RBFs is infrequent, the Centers for Disease Control and Prevention (CDC) says; usually testing for blood levels of lead is done to monitor occupational exposure. But the number of people with RBFs who have toxic blood lead levels (BLLs) may be higher than thought. At BLLs of 10 mcg/dL or greater, hypertension, kidney dysfunction, possible subclinical neurocognitive deficits, and adverse reproductive outcomes have all been documented.

CDC researchers analyzed data from 41 states for 145,811 adults with BLLs of 10 mcg/dL or greater from all causes, reported by the Adult Blood Lead Epidemiology and Surveillance program from 2003 to 2012. Of those, 349 had levels of 80 mcg/dL or greater. RBF-associated cases accounted for 0.3% of all adults with elevated BLLs, but they accounted for 4.9% of adults with BLLs of 80 mcg/dL or greater. The maximum recorded RBF-associated BLL was 306 mcg/dL. In addition, RBF-associated cases were "overrepresented" among people with BLLs of 80 mcg/dL or greater—3.7%, compared with 0.2% of people without RBF-related elevated lead levels.

As of 2004, the researchers say, fewer than 100 cases of lead toxicity caused by RBFs had been reported in the medical literature. They advise asking any patient who has elevated BLLs with an unknown lead exposure source about RBFs. A low index of suspicion could delay diagnosis or even contribute to incorrect diagnoses.

Moreover, BLLs can fluctuate in people with RBFs, they note: Someone with a low BLL at the time of testing can have an increase in BLL and become symptomatic when RBFs migrate, such as into a joint space. The CDC researchers suggest baseline and intermittent BLL tests for people with a history of RBFs.

Source: *Morbidity and Mortality Weekly Report*, February 2017

Artificial Pancreas Moves Closer to Real-Life Option

A major research effort to test and refine the potentially life-changing "artificial pancreas" for the management of type-1 diabetes is now underway and will be joined by three more such projects in 2017 and 2018.

"Managing type-1 diabetes currently requires a constant juggling act between checking blood glucose levels frequently and delivering just the right amount of insulin while taking into account meals, physical activity, and other aspects of daily life, where a missed or wrong delivery could lead to potential complications," said Andrew Bremer, MD, PhD, of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). But that may change soon, as we draw nearer to a functional artificial pancreas: A fully automated system that will sense rising glucose levels, including at mealtimes, and adjust insulin automatically.

The Food and Drug Administration approved a hybrid model of an artificial pancreas in 2016, which still required users to adjust insulin intake. Now, four separate projects have been designed to be the "potential last steps" toward requesting regulatory approval for permanent use of a fully automated system in both pediatric and adult patients. The research studies, the first of which is now recruiting, will look at safety, efficacy, user-friendliness, the physical and emotional health of participants, and cost. The participants will live at home and monitor themselves, going about their normal lives, with remote monitoring by study staff.

"Nearly 100 years since the discovery of insulin," said NIDDK Director Griffin P. Rodgers, MD, MACP, "a successful artificial pancreas would mark another huge step toward better health for people with type-1 diabetes."

Source: National Institutes of Health, February 2017

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One-Time, Nondrug Treatment May Be A Better Choice for Some MS Patients

High-dose immunosuppressive therapy with autologous hematopoietic cell transplant (HDIT/HCT) has had "highly promising" results for patients with relapsing–remitting multiple sclerosis (MS), according to researchers from the HALT-MS trial. In the five-year study, 69% of 24 participants survived without progression of disability, relapse, or new brain lesions—despite taking no MS medications.

Findings published at the three-year mark were encouraging: Event-free survival was 78%. The extended findings suggest that "one-time treatment with HDIT/HCT may be substantially more effective than long-term treatment with the best available medications" for these patients, said Anthony Fauci, MD, Director of the National Institute of Allergy and Infectious Diseases.

The treatment "resets" the immune system, the researchers say. First, doctors collect the patient's blood-forming stem cells, and then they give the patient chemotherapy to deplete the immune system. Finally, they return the patient's stem cells to rebuild the immune system.

Adverse events (AEs) were consistent with those routinely observed after HDIT/HCT. AEs recorded at four and five years were not related to the transplant and, in general, were not considered severe. Three patients died, but their deaths were not related to the study treatments.

Five years later, most trial participants remained in remission and stabilized. Even better, some showed improvements, such as recovering mobility.

Source: *Neurology*, February 2017

When Grief Becomes a Syndrome

Some patients who are suffering long-term grief may be slipping through the health care net.

With data collected in two National Institute of Mental Health–funded treatment studies, researchers used proposed criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (fifth edition) to identify patients with a stress-response syndrome of "persistent impairing grief"—that is, persistent complex bereavement disorder (PCBD), prolonged grief disorder (PGD), and complicated grief (CG). They studied two groups of patients in university-based psychiatric research clinics: 240 grief treatment-seeking participants who scored 30 or higher on the Inventory of Complicated Grief (ICG) and 86 bereaved adults who scored less than 20 on the ICG.

PCBD criteria diagnosed 70% of the first group, PGD criteria identified 59.6%, and CG criteria identified 99.6%. None of the three proposed criteria identified any cases in the bereaved comparison group. Only the CG criteria produced rates of case identification sufficient to be of clinical utility, the researchers say.

Their findings are "virtually identical" to those from the community-based National Military Family Bereavement Study, the researchers say, in which all three criteria sets identified less than 2% of the bereaved military family survey population that scored less than 20 on the ICG.

There are treatments specific to grief, the researchers note. But, as of yet, there's no gold standard for diagnosing persistent impairing grief. They say the solution could lie in using the CG criteria set and modifying decision rules for PCBD or PGD criteria or developing a new group of symptoms and decision rules. However it's done, they conclude, they see a "pressing need" to establish criteria that can lead to correct diagnosis and targeted treatment.

Source: *Psychological Medicine*, March 2017

Pretreatment Imaging May Help Prevent Hodgkin's Lymphoma Recurrence

Advances in radiation treatment have led to better targeting, minimizing the dose to healthy tissue. For patients with Hodgkin's lymphoma, pretreatment scanning with positron emission tomography and computed tomography (PET/CT) has become the gold standard, researchers from the University of Florida say, in determining the extent of Hodgkin's lymphoma. Because the disease may recur at the site of the original cancer, the scans are important to accurately capture its scope. Moreover, the researchers say pretreatment PET/CT scanning may reduce disease progression.

In their study of 37 patients with stage I or II Hodgkin's lymphoma, 31 had PET/CT scans before chemotherapy. Two of the remaining six had PET/CT scans done within five days after chemotherapy was started. Median follow-up was 46 months.

The four-year rate of relapse-free survival was 92%. Patients who did not receive pretreatment PET/CT scans were more likely to have a relapse (67%). Of four recurrences, three were within 12 months of follow-up; one developed five years after treatment.

Among the six patients who did not have a baseline PET/CT scan, all three recurrences were in lymph node regions outside of, but adjacent to, the radiation field. None of the six experienced an in-field treatment failure.

Long-term survivors of Hodgkin's lymphoma are vulnerable to late adverse effects, the researchers note, and that fact is "the impetus behind efforts to reduce radiation exposure to organs at risk." They cite studies that have found that PET/CT scans, compared with using only pretreatment contrast-enhanced CT scans, can alter the staging in 10% to 30% of patients with Hodgkin's lymphoma. Their study, they add, helps support the National Comprehensive Cancer Network guidelines that advise prechemotherapy PET/CT imaging in staging all Hodgkin's lymphoma patients. Not doing complete staging, the researchers say, puts patients at "unnecessary, and in some instances preventable, risk for recurrence."

Source: *Advances in Radiation Oncology* (2017), in press ■