How to Solve Three Puzzles

New knowledge and sophisticated diagnostic techniques are helping doctors recognize early signs of autism, Alzheimer's disease and heart problems in women. Harvard experts report on the advances that are giving patients hope.

DETECTING AUTISM

Early diagnosis of autism is critical because educational programs that build upon a child's strengths and improve social skills may help sculpt the developing brain, minimizing the impact of the illness later in life. But spotting the disorder is hard since there is no test for it, although scientists are slowly uncovering gene abnormalities that make children vulnerable to autism. Last week The New England Journal of Medicine reported that a specific location on chromosome 16 was the site of mutations responsible for some cases of autism.

For now, diagnosis depends on observing a child's behavior. It's a complex process, since no two cases are alike and signs range from mild to severe. Indeed, even though signs of autism may be apparent before their first birthday, most children aren't diagnosed until the age of 3. That makes parents, who are so intimately familiar with their child's behavior, perhaps the most effective diagnostic "tools." The American Academy of Pediatrics recently issued screening guidelines recommending that pediatricians engage parents in evaluating infants for autism. Even babies developing typically, the guidelines say, should be screened at set intervals, such as during the 9-, 18- and 24-month visits.

Healthy infants as young as 6 or 8 months do communicate and respond nonverbally to social cues. Most look up or turn at the sound of their name. By 12 months they typically babble and point at objects. By 16 months they say single words; by 24 months, two-word phrases. In contrast, children with autism seldom make meaningful eye contact or respond to familiar voices. They may never speak. Their play is often repetitive and characterized by limited imagination (neatly arranging crayons instead of coloring with them). Others may simply flap their hands in excitement or disappointment.

On their own, none of these signs means that a child has autism or another developmental disorder. Nevertheless, if your child has any of these signs, he or she merits evaluation. Although no treatments are curative, they can help children learn the skills they need to cope in a normal environment, achieve greater independence and have brighter futures.

SEARCHING: *As researchers hunt for the causes of autism, parents watch their children and worry*

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THE ALZHEIMER'S MYSTERY

Alzheimer's disease, which begins years, even decades, before it causes symptoms, is a quietly ticking time bomb. But until recently doctors had no diagnostic test that could "hear" the ticking. Unfortunately, it didn't matter much that Alzheimer's couldn't be spotted early—at a stage called mild cognitive impairment, or MCI—since there were no treatments. Today, however, there are new diagnostic tests that can detect Alzheimer's at an early stage, and several disease-modifying drugs are in advanced clinical trials.

The brain shrinkage caused by Alzheimer's can now be measured with volumetric magnetic resonance imaging (MRI). This technique takes a series of MRI brain scans and then uses sophisticated mathematical models to analyze the results. Most important, volumetric MRI enables researchers to identify subtle shrinkage in brain areas first affected by Alzheimer's, such as the hippocampus, which is involved in memory.

Another technology in limited clinical use is fluorodeoxyglucose positron emission tomography (FDG-PET). Images produced by FDG-PET reveal patterns of glucose metabolism in the cerebral cortex, the site of abstract thought, reasoning and learning. Because active neurons guzzle glucose for energy, diminished uptake in a specific pattern can denote Alzheimer's. In the research setting, scientists have even used FDG-PET to identify people who do not yet have Alzheimer's but are at risk for developing it, or for developing mild cognitive impairment.

A different kind of PET-scan technology builds on recent discoveries about amyloid plaques and tau tangles, the neuron-killing proteins that accumulate in the brains of Alzheimer's patients. Researchers at the University of Pittsburgh have developed Pittsburgh Compound-B, or PIB. When injected into the blood, this compound binds to amyloid plaques in the brain, allowing them to be detected on PET scans. PET scans with PIB clearly distinguish people with Alzheimer's from healthy people. They may also help identify people with the progressive form of MCI.

Taking a different approach, other researchers are identifying early changes in the levels of particular brain proteins in cerebrospinal fluid. (The clear spinal fluid constantly bathes the brain and spinal cord.) Spinal-fluid levels of the protein tau are typically elevated in Alzheimer's, and an altered version of the tau protein, known as phosphorylated tau, can be detected early in Alzheimer's. Lowered spinal-fluid concentrations of an altered version of beta-amyloid, called Aß42, are typical in Alzheimer's and can also help identify people with mild cognitive impairment who are most likely to progress to Alzheimer's.

FORGETTING: *Alzheimer's patients need earlier diagnoses and new treatments*

Although all these new imaging and biochemical developments are individually promising, the combination of several different imaging tests and biochemical markers may yield the most accurate diagnosis. For example, scientists at the New York University School of Medicine have reported that combining volumetric MRI of the hippocampus with spinal-fluid measures of phosphorylated tau and isoprostane—a marker of oxidative stress—improved diagnostic accuracy in identifying people with mild cognitive impairment who are most likely to progress to Alzheimer's.

We may never reach the stage where we have a single, highly accurate blood test for Alzheimer's, as we do for diabetes. But as the diagnostic technology improves, it may be possible to diagnose Alzheimer's long before symptoms appear. And if the disease-modifying drugs work as intended, that will be very good news indeed.

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HEART DISEASE IN WOMEN

When it comes to diagnosing the most common kind of heart disease, some cardiologists share Henry Higgins's lament in "My Fair Lady": "Why can't a woman be more like a man?" That's because many women don't have the typical symptoms, like crushing chest pain and shortness of breath brought on by physical activity or stress. Instead, they have diffuse discomfort in the chest, unusual exhaustion or depression without an apparent reason. To make matters worse, the tests considered best at diagnosing coronary-artery disease generally don't work as well for women as they do for men. As a result, an alarming number of women with heart disease go undiagnosed and untreated despite repeated visits to the doctor and the emergency room.

Blood flows to heart muscle first through large arteries (the coronary arteries) and then through a branching network of smaller blood vessels. The symptoms of heart disease, in men or women, often result from cholesterol-filled plaques that can slow and completely block the flow of blood to the heart muscle. This type of heart disease, which has been recognized for a century, can be seen with tests such as coronary angiograms (or arteriograms) and, less well, with noninvasive tests such as special CT and MRI scans.

In just the past decade, researchers have learned that many women with chest pain and other symptoms of heart disease have a condition called coronary microvascular disease, which affects the heart's smallest arteries. This fundamentally different form of heart disease is as common and as costly as all female-specific cancers combined, affecting as many as 3 million American women. It affects men, too, but not nearly as often.

Coronary microvascular disease was discovered only recently because, until now, it was not possible to "see" the heart's smallest arteries, which are invisible on a standard angiogram. When microvascular disease occurs, these arteries lose their ability to relax and dilate to increase blood flow to the heart muscle. That's a problem because these tiny tributaries are the ones that must respond most readily when hardworking heart muscle needs more blood. Their inability to dilate on demand limits blood flow to the heart muscle as surely as blockages in larger arteries and causes the same set of symptoms.

Many doctors have not yet heard about coronary microvascular disease. Currently, the most definitive test involves measuring coronary-artery flow reserve or coronary reactivity. It involves threading an ultrathin wire with blood-flow sensors at the tip deep into a coronary artery. Blood flow in the artery is then measured before and after injections of one or more medications that should cause the microvessels to dilate. An alternative, noninvasive way of detecting microvascular disease is with cardiac MRI. This scan measures the amount of blood flowing into the heart muscle before and after the heart is infused with a drug that dilates the microvessels. As with the coronary-reactivity test, if blood flow does not increase, there is disease of the microvessels.

If you are a woman with recurrent chest pain or discomfort, shortness of breath, unexplainable exhaustion and depression, you may need special evaluation even if you have clear arteries on an angiogram. If your doctor says there's nothing wrong, ask for a second opinion at one of a growing number of women's cardiovascular-care centers. You may have coronary microvascular disease.

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