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Fast-Tracking Autism: Diagnosis and Treatment

NYU Langone Medical Center Is Pushing the Frontiers of Autism Diagnosis and Treatment

The Autism Brain Imaging Data Exchange (ABIDE) is providing researchers and clinicians with an important glimpse into the functional organization of the brains of individuals with autism, and these findings are accelerating the pace of discovery and setting the stage for the next generation of autism spectrum disorder (ASD) studies. ABIDE—cofounded and managed by Adriana Di Martino, MD, research director for autism and assistant professor of child and adolescent psychiatry in the Center for... (continued on page 7)

ADHD AND THE STAGES OF LIFE

NYU Langone Psychiatrists Are Leading the Efforts to Diagnose and Treat ADHD through the Life Span

Age-appropriate screens and psychosocial interventions for attention deficit hyperactivity disorder (ADHD) developed by psychiatrists at NYU Langone Medical Center are helping physicians to better diagnose ADHD across the life span.

“The charge is to make an appropriate ADHD diagnosis, use appropriate treatments for the patients, and measure symptoms at baseline and throughout the course of treatment to document any changes,” explains Lenard A. Adler, MD, professor of psychiatry and child and adolescent psychiatry, and director of the Adult ADHD Program at NYU Langone.

The minimum threshold of successful treatment is a 30 percent improvement in the full spectrum of ADHD symptoms, but the goal should be as high as 50 percent, he says. If the patient is not improving, options may include adding a new medication, tweaking dosing of existing medication, and/or implementing another treatment modality.

“All of medicine is driven by outcome measures. That is where our symptom checklist comes in,”... (continued on page 3)

COMPLEX CASE STUDY

Brain Biopsy Findings Link Major Depressive Disorder to Neuroinflammation, Oxidative Stress, and Neurovascular Dysfunction

The patient first experienced depressive mood symptoms at age 15. At that time, he had begun to feel as though he couldn’t experience emotions and was “dead inside.” By age 19, his mood was depressed and irritable often, and he experienced loss of pleasure from activities he previously enjoyed. However, his academic performance and personal achievement, first in school and then at work, remained stellar.

... (continued on page 6)
ADHD and the Stages of Life

(continued from page 1)

he says, “We can’t just say patients are better. We have to show it.”

The clinical instruments developed by the adult and child psychiatry teams are increasingly helping others in the field do just that.

Dr. Adler helped create the World Health Organization Adult ADHD Self-Report Scale (ASRS-v1.1) to better identify adult risk factors. In 2018, new instruments are being assessed in English and Spanish, among other languages. A patient who screens positive for having ADHD, he says, is then given the next step: a longer, 18-item symptom checklist (ASRS-v1.1), which is designed to pick up any of the additional symptoms. “If you don’t know the symptoms, you can’t assess impairment, which is another critical aspect of making the diagnosis,” Dr. Adler says. On the pediatric side, Howard Abikoff, PhD, and the Pandeffect Cohen Child and ADHD Psychiatry and director of the Institute for Attention Deficit Hyperactivity and Behavior Disorders at the Child Study Center at NYU Langone, pioneered with his colleague Richard Gallagher, PhD, the Children’s Organizational Skills Scale (COSS), which can identify problems with organization, time management, and planning. About 50 percent of children with ADHD have organizational deficits that affect their school performance. “We are not just looking at symptoms. We are looking to see what type of functional impairments they cause,” Dr. Abikoff says.

Making the correct diagnosis also involves clinical evaluation. For example, as many as 50 percent of adults with ADHD have one or more comorbidities, such as severe depression or bipolar disorder. “ADHD is present throughout the patient’s whole life, whereas the comorbidities tend to be episodic, so we must look for symptoms that start before the onset of the comorbidity or that persist after the comorbidity is quiescent,” Dr. Adler says. “The clinician has to take a longitudinal retrospective history because the motes of ADHD lie in childhood.”

Collateral information can also help doctors sift through layers of comorbidities and make a definitive diagnosis of ADHD. “A good clinician, if they obtain the right information from the right sources, is better able to make the differential diagnosis,” says Dr. Abikoff. Once ADHD is properly diagnosed, medication is only one part of an effective treatment strategy. “Medications can take care of the symptoms of inattention, distractibility, and restlessness, but they are often not as effective for treating executive dysfunction,” says Dr. Adler. He is now validating the adult correlate of a skills training psychosocial intervention that seeks to improve higher-level cognitive function, working memory, time management, emotional control, and other skills of executive function. “We are trying to create an easier-access, five-session manual based on some of the principles of cognitive behavioral therapy that can be utilized by all healthcare providers, not just psychiatrists.”

Dr. Abikoff’s group is field testing an organizational skills training (OST) program that he and Dr. Gallagher developed and that can be used by therapists across multiple settings. The OST program uses task analysis and behavioral skills training to teach effective organizational strategies to help third-, fourth-, and fifth-grade diagnosed with ADHD who are experiencing difficulties with organization, time management, and planning tasks. Results from a large study funded by the National Institute of Mental Health indicated that about 60 percent of children treated with the OST program improved to the point that their organizational functioning was no longer impaired, and this led to improvements in academic performance. Patients who completed a contingency management program also showed marked improvement. The next step is to determine which method works best in which children and why.

“The field of healthcare is moving toward personalized medicine. Our approach to children and families is highly individualized care based on evidence-based practice,” says Glenn S. Hirsch, MD, assistant professor of child and adolescent psychiatry and vice chair for clinical affairs at NYU Langone’s Child Study Center. “As we continue on this journey, we will take into account all aspects of the patient’s symptoms and the symptoms’ impact on their world, and we carefully tailor our treatment to the needs of the individual and their family.”
A clinician’s recognition that a child’s symptoms may have a traumatic origin can be life changing for the child. Once this origin is recognized, a course of treatment can be implemented that gets to the bottom of the child’s problems and sets the stage for a happier, healthier, and more successful life. Traumatic stress in children may present like other psychiatric illnesses, and the failure to recognize it can have tragic consequences.

“If you don’t ask the right questions to understand the context of the child’s emotional state, it’s easy to give a diagnosis that misses the nature of their core problem,” explains Glenn Saxe, MD, the Arnold Simon Professor of Child and Adolescent Psychiatry, chair of the Department of Child and Adolescent Psychiatry, and director of the Child Study Center at NYU Langone Medical Center. “You might misinterpret their behavior disruptions in school, but if no one is looking for the patterns, the child may receive a medical solution to the problem, but there isn’t.”

“An assessment often should involve finding out what is really happening in the child’s environment,” Dr. Saxe says. “There is no rhyme or reason to the child’s behavior. It diminishes ongoing stresses and threats in the social environment through the use of skill-based psychotherapy, home and community-based care, advocacy, and/or medication.”

“Often nothing is working because there are things going on that no one is asking about. Ask the questions. Be curious. We need to try to understand the reality of these children’s lives.”

—Glenn Saxe, MD

“An assessment often should involve finding the most horrific experience and attaching it to symptoms,” Dr. Havens says. Instead, these kids are typically given antipsychotic medications.

“It is akin to coming into the emergency room with a heart attack and leaving with a diagnosis of diabetes and a prescription for insulin. If you give them a pill, they will think there is a medical solution to the problem, but there isn’t.”

Dr. Saxe adds that clinicians often need to dig deep to find out what is really happening in the child’s environment,” Dr. Saxe says. “There is no rhyme or reason to the child’s behavior. It diminishes ongoing stresses and threats in the social environment through the use of skill-based psychotherapy, home and community-based care, advocacy, and/or medication.

“We give clinicians in any setting the skills, tools, and training to do it without us, and this includes scaling up and sustaining their program,” says Dr. Saxe. His department recently received three grants totaling $7 million to improve the way traumatized children in the United States, including those in the juvenile system and the foster care/child welfare system, are assessed, diagnosed, and treated.

Child Psychiatrists at NYU Langone Raise the Standard of Care for Treating Complex Childhood Trauma

The stakes are high. One out of three children in the United States is considered overweight or obese. “If a child is obese, there is a 35 percent chance that he or she will have metabolic syndrome,” Dr. Convit explains. “The brain makes more BDNF when you exercise. BDNF is essential for the maintenance and repair of the brain, and we know that BDNF is lower in people who are obese and have metabolic syndrome.”

Another major player in this area is brain-derived neurotrophic factor (BDNF). “BDNF is critical for weight loss,” Convit says. “If a child is obese, there is a 35 percent chance that he or she will have metabolic syndrome.”

“The more overweight that a child is, the more his brain and his behavior are affected,” Dr. Saxe says. “Their brains are not firing on all pistons,” he notes. “Ask the questions. Be curious. We need to try to understand the reality of these children’s lives.”

Photo credit: NYULMC

Cognitive Impairment: a Hidden Consequence of the Childhood Obesity Epidemic

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Cognitive Impairment: a Hidden Consequence of the Childhood Obesity Epidemic

Research at NYU Langone Medical Center Unravels Obesity’s Effects on the Brain

Jennifer Convit, MD, the Lucius N. Littauer Professor of Psychiatry and chair of the Department of Psychiatry at NYU Langone, lauds this population health-based approach. “As psychiatrists, we need to work with others to get kids eating less and moving more and work together with primary care doctors, politicians, and government,” he says. “We need to take psychiatry outside of the clinic because psychiatrists studying mind, brain, and behavioral issues can make a major contribution to population health.”

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Photo credit: NYULMC

Cognitive Impairment: a Hidden Consequence of the Childhood Obesity Epidemic

Research at NYU Langone Medical Center Unravels Obesity’s Effects on the Brain

Translational research taking place in the Brain, Obesity, and Diabetes Laboratory (BODyLab) of NYU Langone Medical Center is helping scientists gain a better understanding of one of the most underappreciated consequences of the child obesity epidemic in the United States— the effects of obesity and the metabolic syndrome on the brain.

Antonio Convit, MD, professor of psychiatry and medicine, and director of BODyLab, and colleagues are quantifying physiologic brain changes seen on magnetic resonance imaging (MRI) scans of obese children with metabolic syndrome. So far, they have noted hippocampal shrinkage and changes in the white matter, which may be associated with the cognitive impairments that they have documented in this population.

Dr. ConVit’s research, recently published in Pediatrics, found that such children perform worse on memory and spelling tasks and on tests of their overall intellectual functioning. “Their brains are not firing on all pistons,” Dr. Convit says. “The catch is that when you stop exercising, you lose these benefits. Getting this population to comply with lifestyle changes over the long haul is a challenge,” he says. “Once you gain weight, your body is working against you. It’s a real struggle to lose.”

While the research in the lab continues, Dr. Convit is also taking his findings into New York City public schools to help identify earlier children at risk of type 2 diabetes, as part of The BODy Project (Banishing Obesity and Diabetes in Youth). At-risk kids receive user-friendly reports of their medical results along with information for the whole family about how to turn things around before the child develops type 2 diabetes. “The MRI studies should also help elucidate some of the pathways affected by insulin resistance and obesity, and lead to new treatments to help mitigate these risks,” Convit says.

Charles Marmar, MD, the Lucius N. Littauer Professor of Psychiatry and chair of the Department of Psychiatry at NYU Langone, lauds this population health-based approach. “As psychiatrists, we need to work with others to get kids eating less and moving more and work together with primary care doctors, politicians, and government,” he says. “We need to take psychiatry outside of the clinic because psychiatrists studying mind, brain, and behavioral issues can make a major contribution to population health.”

Another major player in this area is brain-derived neurotrophic factor (BDNF). “BDNF is critical for weight loss,” Convit says. “If a child is obese, there is a 35 percent chance that he or she will have metabolic syndrome.”

“Another possibility is problems with vascular reactivity. The endothelial cells may not work as effectively in obese children with metabolic syndrome or prediabetes,” Dr. Convit says. “Another possibility is problems with vascular reactivity. The endothelial cells may not work as effectively in obese children with metabolic syndrome or prediabetes,” Dr. Convit says. “Another possibility is problems with vascular reactivity. The endothelial cells may not work as effectively in obese children with metabolic syndrome or prediabetes,” Dr. Convit says. “Another possibility is problems with vascular reactivity. The endothelial cells may not work as effectively in obese children with metabolic syndrome or prediabetes,” Dr. Convit says. “Another possibility is problems with vascular reactivity. The endothelial cells may not work as effectively in obese children with metabolic syndrome or prediabetes,” Dr. Convit says. “Another possibility is problems with vascular reactivity. The endothelial cells may not work as effectively in obese children with metabolic syndrome or prediabetes,” Dr. Convit says. “Another possibility is problems with vascular reactivity. The endothelial cells may not work as effectively in obese children with metabolic syndrome or prediabetes,” Dr. Convit says. “Another possibility is problems with vascular reactivity. The endothelial cells may not work as effectively in obese children with metabolic syndrome or prediabetes,” Dr. Convit says. “Another possibility is problems with vascular reactivity. The endothelial cells may not work as effectively in obese children with metabolic syndrome or prediabetes,” Dr. Convit says.
At age 29, the patient found himself easily fatigued despite excessive sleep. His energy was persistently low. His capacity to be productive at work was waning. He was psychologically hospitalized for a major depressive episode and was treated aggressively with a combination of psychotherapy and pharmacotherapy, which continued going forward.

By age 35, the patient could not sustain work because of persistent mood symptoms and cognitive dysfunction. Over the next four years, an MRI of the brain, neuropsychological testing, an EEG, and sleep studies were performed. The results of these tests were unremarkable until the patient was 38, when he was told that he was suffering neurological complications of Lyme disease. Before being referred to NYU Langone, he was treated elsewhere with antibiotics, acyclovir, over-the-counter supplements, transcranial magnetic stimulation, and hyperbaric oxygen. All were of no benefit.

At age 39, after 10 years of treatment, he terminated psychotherapy. He then sought neuropsychiatric evaluation with Scott Hirsch, MD, assistant professor of neuropsychology and psychiatry at NYU Langone Medical Center. On presentation, his effect was dysphoric, and he was easily frustrated. He demonstrated numbing and expressed intense anxiety and hopelessness. He had lost interest in most of the activities he had previously enjoyed. He exhibited slow processing speed, yet seemed highly intelligent. Segmental neurological examination was unremarkable. There was no evidence of myoclonus, dystonia, dyskinesia, or tics.

Despite the patient’s cognitive complaints, neuropsychological testing revealed high scores on all measures (90th to 99.7th percentile) for further evaluation. On presentation, his effect was dysphoric, and he was easily frustrated. He demonstrated numbing and expressed intense anxiety and hopelessness. He had lost interest in most of the activities he had previously enjoyed. He exhibited slow processing speed, yet seemed highly intelligent. Segmental neurological examination was unremarkable. There was no evidence of myoclonus, dystonia, dyskinesia, or tics.

Comprehensive serological and cerebrospinal fluid assays for infectious agents, systemic autoimmune diseases, and antineuronal antibodies were all unremarkable.

The clinical presentation and history were consistent with the working diagnosis of major depressive disorder (MDD). Given the severity of the symptoms, Dr. Hirsch referred the patient to Norman Sussman, MD, professor of psychiatry and director of NYU Langone’s Treatment-Resistant Depression Program. Because of the patient’s extensive history of unsuccessful treatment with antidepressant medications, treatment was aimed at providing symptomatic relief using neuropsychiatric medications with reported benefits in treating mood disorders.

The patient had been taking the antidepressants fluoxetine and bupropion, as well as quetiapine, clozapine, and an amphetamine. Bupropion, which is known to cause cognitive impairment, was discontinued. Although clozapine also impairs memory and reaction times, it was not stopped because the patient reported dense, significant symptom relief from the drug. After the first visit, Dr. Sussman added memantine to the regimen with the rationale that its glutamatergic effects could prove helpful.

However, given the abnormal nonspecific brain MRI and SPECT imaging findings, there was also concern about a low-grade encephalopathic process, such as innumerable autoimmune encephalitis, that might be treatable. As a result, the patient was also referred to Souhel Najjar, MD, clinical associate professor of neurology at NYU Langone’s Comprehensive Epilepsy Center, for further evaluation.

Accordingly, a brain biopsy was obtained and was used to exclude an encephalopathic process. Histological examination showed mild nonspecific inflammation without lymphocytic infiltration, with mild perivascular macrophage histiocytic infiltration and mild to moderate subcortical astrogliosis. Ultrastructural analysis revealed lipofuscin granule accumulation exclusively within the neuraxial unit, indicative of oxidative stress leading to blood-brain barrier dysfunction. While the medical literature had previously documented increased central nervous system oxidative stress in MDD, this was the first demonstrated evidence of oxidative injury in the neurovascular endothelium. Because of the confirmed presence of inflammation, intraneuronal immunoglobulin (IVG) pulse therapy was started and continued twice weekly for nine months. Three months after initiation of IVG, intraneuronal myelinolysis was started because of its anti-inflammatory and antidepressant effects demonstrated in animal models of depression.

Ten months after initiation of IVG, a repeat SPECT scan showed complete normalization of frontal hyperperfusion. Of note, the psychoticregimen remained essentially constant over this 10-month period. At the time of a neuropsychiatric reevaluation 13 months after starting IVG, the patient reported significant improvement in his mood and much better control of his anxiety. His wife reported a positive personality change in her husband. He was much more active in general and more appropriately engaged with his family. He was more interested in socializing, and he became an active participant in raising his child. In fact, he was excited to report that he and his wife were expecting a second child. Motivation and energy were reported as better.

Reductions in the MADRS (from 25 to 15), the BDI-II (27 to 15), and the BAI (22 to 3) were also noted. Eighteen months after starting IVG, the patient reported sustained improvement in mood symptoms he could remember; his MADRS score was 8. Of note, in the Treatment-Resistant Depression Program, Dr. Sussman was documenting the patient’s clinical course separately for further evaluation.

For more information, see the case study report published in Biol Psychiatry 2013 Sept 27.

Neuropsychiatric evaluations with NYU Langone’s Child Study Center provides resting state functional magnetic resonance imaging (fMRI) data on more than 1,300 people with autism from 17 international sites along with corresponding structural MRI and phenotypic information from 539 individuals with ASDs and 573 age-matched typical controls. The largest imaging sample available through open access sharing is helping to take research out of the traditional silos so that it can better foster discovery and innovation.

Since it began in 2012, the registry has grown to include several significant research papers and poster presentations. One study published in June 2013 in Molecular Psychiatry helped to elucidate the dysconnectome models of autism by illustrating concurrent hyper- and hypoperfusion in different regions of the brains of individuals with autism. Specifically, MRI images from the ABIDE registry showed hypoconnectivity in the brain’s cortico-subcortical and interhemispheric regions, and hyperconnectivity in the subcortical region, namely, the thalamus. The thalamic centers have always been considered important in autism, but these studies are highlighting the role of other circuits, like the thalamus, Dr. Di Martino says.

“There are too many neurons and not enough pruning of the pathways in the brains of people with autism, which disrupts neural circuitry,” adds Melissa Nishawala, MD, assistant professor of child and adolescent psychiatry and medical director of the Autism Spectrum Disorders Clinical and Research Program at NYU Langone’s Child Study Center. “Fostering state fMRI shows these connections, and it looks like noise until you tune in and a pattern appears, and then . . . wow! Even when a child is doing nothing, their social centers, motor centers, and language centers are communicating with each other. This is important for coordinating, gesturing, speaking, and socializing.”

The hope is that these studies will provide insights into the mechanism of the pathophysiology responsible for autism and ultimately lead to the development of more effective therapies that can be implemented earlier than is currently possible. “The earlier we make the diagnosis, the sooner we can do something about autism,” Dr. Nishawala says.

There is progress even as ABIDE data are culled, says Dr. Nishawala. Child psychiatrists and autism specialists at NYU Langone are helping families move beyond the label and toward therapies that work. “You can’t just say a kid has autism. You have to look at the other things going on. There are many choices for helping each child,” she says. “We hope in the future to use brain scans to predict which treatment will be most beneficial to a child with autism and to track the child’s progress.

“The challenge in treating autism is to identify the strengths and weaknesses in each patient and use the best therapies available for them,” Dr. Nishawala says. The Child Study Center offers several types of therapies in addition to gold-standard applied behavior analysis, including parent training response treatment, the Early Start Denver Model, and others. The therapists at the center match these treatments to individual needs based on their strengths, weaknesses, and needs.

For more information, visit www.NYULMC.org/psychiatry or www.aboutourkids.org

Photo credits: Mary Kouw

Tracking Autism: Diagnosis and Treatment

Department of Psychiatry: 646.754.4858 • Department of Child and Adolescent Psychiatry: 212.263.6622

For more information, visit www.NYULMC.org/psychiatry or www.aboutourkids.org
The NYU Langone Medical Center Department of Psychiatry recently published research on the effects of folate supplementation in schizophrenia, marking one of the first successful uses of personalized medicine in psychiatry. Ongoing work in this area may change the way the medical profession views psychosis.

"NYU Langone is in the forefront of the study of biomarkers, early intervention, and personalized medicine in psychosis," says Donald Goff, MD, the Marvin Stern Professor of Psychiatry and vice chair for research in the Department of Psychiatry at NYU Langone. According to Dr. Goff's newest study, published in *JAMA Psychiatry*, supplementation with folate and vitamin B12 improved the prominent negative symptoms of schizophrenia in individuals, but only those with low folate levels who also had genes for less active forms of folate hydrolase and methylene tetrahydrofolate reductase enzyme at baseline.

"One genotype that achieved statistical significance on its own was folate hydrolase, which is a rate-limiting step in absorption of folate from the gut," Dr. Goff says. "Subjects with the most active form of folate hydrolase were the most likely to benefit—possibly because they were better able to absorb the supplemental folate."

Dr. Goff's earlier work, with his collaborator Joshua Roffman, MD, identified the link between folate deficiency and negative schizophrenia symptoms, and this new study takes this work a step further by showing who is most likely to respond to folate supplementation.

Dr. Goff and his team are now using molecular imaging to identify biomarkers and biochemical changes that are indicative of treatment response in patients with newly diagnosed, first-episode psychosis. In this randomized study, participants will receive standard care with an antidepressant or standard care plus placebo.

"The hope is if we intervene early enough with antidepressants in the right patients, we may have a major impact on the long-term course of psychosis," Dr. Goff says.

Dr. Malaspina’s work is also helping to broaden the context in which the medical profession sees psychosis. Research has shown that psychosis increases risk for metabolic syndrome, cardiovascular disease, and diabetes. These risks cannot be explained by unhealthy behaviors such as smoking. “These contribute to the additional risk, but the earlier mortality is not explained by these behaviors. It just transcends them,” she says.

The new theory is that psychiatric disease may be the earlier manifestation of compromised microvasculature and that it is likely a whole body disorder, Dr. Malaspina explains. “Psychosis may be the first presentation of systemic illness, not only a brain disease.” The work, if validated, will help remove the stigma associated with mental illness.

Dr. Malaspina discusses this research in the December 2013 issue of the *Journal of the American Psychiatric Association.*