

CASE MANAGEMENT:

## Autistic disorder and Asperger's disorder

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*Jack, a 12-year old male with a diagnosis of Asperger's disorder and an IQ of 125, presented with three problematic behaviors: (1) an intense, all-encompassing preoccupation with pheasants that greatly interfered with his attempts at reciprocal social interaction; (2) problems getting up in the morning and subsequent tantrums and refusal to go to school because of late nights spent reading and watching television shows about pheasants and surfing the internet for additional information; and (3) extreme difficulty maintaining friendships with his peers because of his single-minded focus.*

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### OVERVIEW OF AUTISTIC DISORDER AND ASPERGER'S DISORDER

**A**utistic disorder, or autism, was first described by Leo Kanner in 1943. Today, autism and Asperger's disorder are classified as two of the five pervasive developmental disorders (PDDs), all of which are characterized by varying degrees of impaired social interactive and communication skills and restrictive, repetitive and stereotyped behaviors.<sup>1</sup>

“Disturbances in social relatedness in persons with autism or Asperger's disorder

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1. McDougle CJ, Hulvershorn L, Erickson CA, Stigler KA, Posey DJ. Autistic syndromes. In: Abramowitz JS, McKay D, Taylor S, eds. *Clinical Handbook of Obsessive-Compulsive Disorder and Related Problems*. Baltimore: The Johns Hopkins University Press; 2008:238-256.

can present in many ways, including poor eye contact and gaze aversion, difficulty in initiating or responding to social interaction, inability to ‘read’ nonverbal cues (eg, facial expressions and body language), and social withdrawal or inappropriate interaction, such as standing too close to another person,” explains Christopher McDougle, MD, Albert E. Sterne Professor and chairman of the Department of Psychiatry. “Language delay is common in autism and is often one of the first symptoms noticed by parents. Babies usually begin speaking by about one-year of age, but about half of all persons with autism never develop appropriate verbal communication. Among those who do talk, echolalia, the parroting back of words, may be a feature of their speech.”

Some of the restrictive and repetitive behaviors associated with autism are hand-flapping, rocking, and toe-walking. In addition, affected children may engage in extensive rituals, such as lining up toys or other objects and spinning, either objects or them-

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*Statements of Disclosure of Relevant Financial Relationships have been obtained from Dr. Christopher McDougle. Dr. McDougle has disclosed that he has received honorarium from Bristol-Myers Squibb Co. and received a consulting fee from F.Hoffmann-La Roche Ltd.*

#### OBJECTIVES

After reading this article, the reader should be able to:

- Summarize the three core disturbances that characterized the pervasive developmental disorders (PDDs).
- Compare and contrast autistic disorder and Asperger's disorder.
- Describe some of the early signs of autism.
- Discuss the nonpharmacologic and pharmacologic interventions used in the management of PDDs.

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selves. Another prominent feature of autism is the imperative for “sameness.”

“Autistic children need and demand absolute consistency in their environment,” Dr. McDougle stresses. “The slightest change in routine—altered mealtimes or taking a different route to school, for example—can be extremely upsetting.”

Mental retardation is present in approximately 75 percent of all children with autism.<sup>2</sup> In contrast, individuals with Asperger’s disorder have normal IQs as well as normal language development. Like Jack in the case vignette, they often become fixated on a subject that is age-inappropriate and/or in which their peers have no interest. Because of this intense preoccupation with and knowledge of one topic, young children with Asperger’s disorder are often initially labeled as “geniuses” or “little professors.”

## EPIDEMIOLOGY AND ETIOLOGY

The prevalence of autism is estimated to be 13 per 10,000, and it is four times more common in males than in females.<sup>2</sup> The rate of Asperger’s disorder is 2.6 per 10,000. Experts agree that autism prevalence rates are rising because of growing awareness of the problem. However, they believe incidence has not markedly increased in recent years.

Although the etiology of autism is unknown in most cases, it appears to be multifactorial. Genetics almost certainly play a major role, and several, as yet unidentified, genes are likely involved.

“Fragile X syndrome accounts for one to two percent of autism cases, and other chromosomal abnormalities are detected in

2. Stigler KA, Erickson CA, Posey DJ, McDougle CJ. Autism and other pervasive developmental disorders. In: Findling RL, ed. *Clinical Manual of Child and Adolescent Psychopharmacology*. Washington, DC and London: American Psychiatric Publishing, Inc; 2008:265-300.

Table 1. Drugs used in the management of autism and other PDDs <sup>2</sup>
Atypical antipsychotics
Selective serotonin reuptake inhibitors
Serotonin and norepinephrine reuptake inhibitors
Alpha2-adrenergic agonists
Psychostimulants
Atomoxetine (a selective norepinephrine reuptake inhibitor)
Mood stabilizers
Glutamatergic agents

another five to 10 percent of cases,” reports Dr. McDougle. “Blood testing is important whenever autism is suspected, as positive results can have important implications not only for the patient but also for other family members who may carry the genetic or chromosomal defect.”

An increased prevalence of autoimmune disease in parents, especially mothers, has been observed in children with autism in some studies.<sup>3</sup> Research has shown genes long implicated in disorders such as lupus erythematosus and rheumatoid arthritis are significantly increased in autistic popula-

3. Sweeten TL, Bowyer SL, Posey DJ, Halberstadt GM, McDougle CJ. Increased prevalence of familial autoimmunity in probands with pervasive developmental disorders. *Pediatrics*. 2003;112(5):e420.

tions, although a definitive relationship has not been established.

“Autoimmunity or chronic immune activation could help explain some peripheral biochemical as well as neurochemical abnormalities observed in autistic patients, such as hyperuricemia, iron deficiency and elevated blood levels of serotonin,” says Dr. McDougle.

Despite the concerns of some parents, scientific research has found no link between vaccinations and autism. Dr. McDougle points out autism typically is diagnosed at 12 to 18 months, which coincides with many childhood immunizations and leads to a false sense of cause and effect. Parental suspicion is now so high, however, that increasing numbers of children are going unvaccinated. As a result, public health officials fear one of the most important advances in medical history will be undermined.

## SIGNS, SYMPTOMS, AND DIAGNOSIS

To establish the diagnosis of autism, problems in at least one of the areas of socialization, communication and restricted behavior must be present before the child reaches the age of three years.

“The early diagnosis of autism is suggested by the absence of normal development rather than the presence of specific symptoms,” points out Dr. McDougle. “A mother will often report that her one-year-old won’t cuddle, hasn’t started talking, and doesn’t turn around when his or her name is called. At about age two years, autistic children begin engaging in repetitive and ritualistic behaviors. And by the time they enter preschool, these youngsters can be found playing by themselves on the periphery rather than joining in with their peers.”

## TREATMENT

Accumulating evidence indicates early intervention using a multimodal approach results in improved outcomes for most youngsters with autism.<sup>4</sup>

### *Nonpharmacologic Interventions*

“Intensive speech and language therapy, ideally one-on-one in a child care center and at home with private tutors, is an essential component of every autism treatment regimen,” Dr. McDougle stresses. “Social skills are developed by encouraging the child to interact with siblings and normal youngsters. Individual, group counseling and training may also be used to teach children how to act in a more socially acceptable manner.”

Physical and occupational therapies are important interventions for helping a child develop gross and fine motor skills. In addition, many children with autism are high-

ly attuned or even painfully sensitive to certain sounds, textures, tastes and smells, and occupational therapy can reduce such hypersensitivity. Educating caregivers about behavioral management techniques is also useful and may decrease the need for medication.

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*Before visiting our clinic, Jack had had previous attempts at pharmacotherapy, including a three-month trial of the central nervous system stimulant methylphenidate at a maximum daily dose of*

*54 mg. While the medication helped with inattention, its use led to increased irritability, a worsening of repetitive thoughts and behavior, and the emergence of motor tics, all of which resolved upon drug discontinuation. Jack’s response to methylphenidate is not surprising, as research has shown that compared with typically developing children with attention deficit hyperactivity disorder, psychostimulants are less effective and are associated with a higher frequency of adverse effects in youth with PDDs.<sup>2</sup>*

## SIDEBAR

### The Christian Sarkine Autism Treatment Center



The Christian Sarkine Autism Treatment Center at Riley Hospital for Children on the Indiana University-Medical Center campus is one of two academic and research programs dedicated to autism in the state of Indiana. The Center is dedicated to bringing the most current and accurate information to its mental health professionals and students. It is committed to helping children and adults with autism and related disorders achieve their potentials and participate as fully as possible in family, school and community life.

The center received \$1.86 million in federal funding for autism at the close of the 106th Congress (1999-2001), facilitating construction of a new facility and expansion of clinical services and research efforts. Today, the center actively treats more than

600 children, making it one of the busiest in the country. In addition, it is one of only three US sites participating in a National Institute of Mental Health-funded project focused on medication treatment and parent management training development for individuals with autism.

Interventions used at the center are based on the individual goals and family objectives. Treatment typically involves medication management, speech and language intervention and/or counseling, and behavioral strategies and reflects the most recent and empirically-supported approaches to management. Individuals and families may also have the opportunity to become involved in research projects. Services may be provided in a time-limited or ongoing fashion. ■

4. Filipek PA, Accardo PJ, Baranek GT, et al. The screening and diagnosis of autistic spectrum disorders. *J Autism Dev Disord.* 1999;29(6):439-484.

*Our treatment team initially prescribed the selective serotonin reuptake inhibitor (SSRI) sertraline 25 mg/day, increased to 50 mg after one week. Five days after the dose increase, Jack's mother reported heightened agitation and hyperactivity.*

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#### Pharmacotherapy

In addition to the core features of autism, many patients have associated target symptoms, including hyperactivity/inattention, repetitive interests/activities, sleep disturbances and irritability, Dr. McDougle describes. Irritability can manifest as aggression and lead to physical injury to the patient or others, destruction of property and severe tantrums. Medication can reduce these maladaptive behaviors, allowing patients to obtain maximal benefits from educational services and other nonpharmacologic interventions.

Atypical antipsychotics have emerged as first-line pharmacologic treatment for irritability and associated dysfunctional behaviors in children and adolescents with autism and other PDDs.<sup>5</sup> To date, risperidone is the only drug approved for this purpose by the US Food and Drug Administration. Approval was based on the results from two double-blind placebo-controlled studies that demonstrated the beneficial effects of risperidone in patients aged five to 16 years.

Other drugs that may be helpful in the management of autism and other PDDs are presented in Table 1 on page A2.

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5. McDougle CJ, Stigler KA, Erickson CA, Posey DJ. Atypical antipsychotics in children and adolescents with autistic and other pervasive developmental disorders. *J Clin Psychiatry*. 2008;69 Suppl 4:15-20.

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*Children with PDDs appear to be more susceptible than other youngsters to SSRI side effects, including behavioral activation and agitation.<sup>1</sup> Jack's physician discontinued sertraline and started him on a trial of risperidone. Jack was also enrolled in weekly cognitive therapy sessions, where he learned to use phrases such as, "I'll do something else, think about other things, talk to someone else," when he was exposed to television programs featuring pheasants. In addition, Jack started keeping a journal and described how his excessive talk about pheasants was socially inappropriate.*

*After one month of combined treatment, including a dose titration up to 1 mg of risperidone at bedtime, Jack showed some positive effects that included less time spent looking up information about pheasants and a decreased frequency of aggressive outbursts when others interfered with his pursuit of such information. After two months of therapy, the aggressive behavior surrounding his obsession ceased. Jack's dose of risperidone was gradually increased over the next 10 months to 1 mg twice daily. Because weight gain is a well-known side effect of some atypical antipsychotics, his body weight was monitored regularly, and it remained developmentally normal during the course of risperidone treatment. Jack continues to be very interested in pheasants, but he is willing to be redirected away from his pursuit of pheasant-related material.*

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#### **PROGNOSIS**

"Most children with autism and mental retardation will not have 'normal' lives, and it is critical that parents come to terms with this early on," says Dr. McDougle. "They can be reassured, however, that while their children will be different, they will be happy and functional."

Some autistic children attend regular school and are assisted by aids; others are enrolled in special education. Most will earn a high school "certificate," although they often remain in school until age 22, during which time they may receive vocational training. Children with Asperger's disorder sometimes attend college, but those with autism are highly unlikely to do so. Nonetheless, Dr. McDougle says children with autism may have special talents, such as art or music, that can be fostered and developed, which gives them self-esteem and pleasure.

"Most adults with autism eventually leave home—and they should do so before their parents become old or die," comments Dr. McDougle. "Typically, they live in group homes with other autistic people and never marry, nor do they want to, because of their lack of social skills or interest.

When a child is diagnosed with autism, parents may tend to focus much of their attention on that child, ignoring other children in the family as well as their relationship with one another. Many families go into debt paying for intensive therapy or autism "cures" that cannot significantly alter the course of the disorder.

"In terms of social impairment, children may improve as they get older because of normal brain changes, interventions and learning from others," says Dr. McDougle. "But the condition is pervasive, and it never disappears. In some ways, autism is more our problem than a problem for patients. Autistic children are doing what they want—and we have to accept that. We as a society need to adapt to their uniqueness rather than vice versa." ■

#### **Errata in July/August 2008**

*In the case study on page A5, last paragraph, the next to last line should read "monitored over the years and has had" not "maintained over the year and has had."*



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**Research Interests:**

Neuropsychopharmacology of childhood-onset neuropsychiatric disorders including autistic disorder and other pervasive developmental disorders, obsessive-compulsive disorder, and chronic tic disorders

**Recent Publications:**

McDougle CJ, Scahill L, Aman MG, McCracken JT, Tierney E, Davies M, Arnold LE, Posey DJ, Martin A, Ghuman JK, Shah B, Chuang SZ, Swiezy NB, Gonzalez NM, Hollway J, Koenig K, McGough JJ, Ritz L, Vitiello B: "Risperidone for the core symptom domains of autism: Results from the study by the Autism Network of the Research Units on Pediatric Psychopharmacology." *Am J Psychiatry* 162:1142-1148, 2005.

Posey DJ, Aman MG, McCracken JT, Scahill L, Tierney E, Arnold LE, Vitiello B, Chuang SZ, Davies M, Ramadan Y, Witmer AN, Swiezy NB, Cronin P, Shah B, Carroll DH, Young C, Wheeler C, McDougle CJ: "Positive effects of methylphenidate on inattention and hyperactivity in pervasive developmental disorders: An analysis of secondary measures." *Biol Psychiatry* 61(4):538-544, 2007.

Erickson CA, Posey DJ, Stigler KA, Mullett J, Katshke AR, McDougle CJ: "A retrospective study of memantine in children and adolescents with pervasive developmental disorders." *Psychopharmacology* 191:141-147, 2007.

**INDIANA UNIVERSITY MELVIN AND BREN SIMON CANCER CENTER ADVANCES PROSTATE CANCER RESEARCH WITH PROGRESS**

Noah Hahn, MD, assistant professor of medicine in the Division of Hematology/Oncology at the IU School of Medicine and a member of the IU Melvin and Bren Simon Cancer Center, and his colleagues are directing a study called PROGRESS (PROstate Cancer – Genetic Risk Evaluation of Single nucleotide polymorphisms Study) to identify genetic and environmental risk factors which contribute to the development of prostate cancer and affect responses to therapy.

Dr. Hahn said new technology will allow IUSM researchers to examine the role of more than 500 genetic mutations and environmental toxic effects simultaneously. Previous studies have examined large sets of genes, but never in conjunction with data measuring how environmental factors impact prostate cancer risk.

The team hopes to identify the "high-risk genetic signature" that raises an individual's risk for aggressive prostate cancer. Dr. Hahn adds that by identifying such a signature, improved screening and prevention programs can be developed and implemented for those men at greatest risk.

For additional information about the PROGRESS study call (317) 274-3655.

**IU SCIENTIST RECEIVES AWARD TO STUDY SURROGATE DECISION MAKING FOR OLDER ADULTS**

Alexia Torke, MD, MS, assistant professor of medicine and research scientist with the Regenstrief Institute and the IU Center for Aging Research, was named a 2008 Hartford Geriatrics Health Outcomes Research Scholar.

One of only four recipients honored nationwide, Dr. Torke was selected for the prestigious award by a committee of nationally prominent academic physicians.

As a Hartford Geriatrics Health Outcomes Research Scholar, she receives a two

year, \$200,000 award which she will use to conduct a large study of surrogate decision making for hospitalized older adults.

Dr. Torke's research focuses on ethical aspects of medical decision making for older adults, including surrogate decision making for patients with dementia and other forms of cognitive impairment. Her long term goal is to improve the process and outcomes of decision making for older adults who cannot make their own medical decisions.

**NEW THINK TANK TACKLES HEALTH POLICY AND PROFESSIONALISM ISSUES**

Quick turnaround research is the goal of the Center for Health Policy and Professionalism Research (CHPPR), recently created as an innovative think tank at IUSM.



Aaron Carroll, MD, MS

Established as an independent objective source of health information, the new center translates research into practice in a timeframe that satisfies the needs of policymakers and other decision makers.

Earlier this year, the new center published the results of a national survey of physician opinion on national health insurance in the *Annals of Internal Medicine*. The largest survey ever of American physicians' opinions on health-care financing, it found that 59 percent of doctors support government legislation to establish national health insurance while only 32 percent oppose it.

CHPPR is establishing the capacity to rapidly deploy national phone and mail surveys. Results of these types of CHPPR studies can be communicated directly to decision makers as well as disseminated through the traditional channels of peer-reviewed publications and professional meetings.

Aaron Carroll, MD, MS, associate pro-

fessor of pediatrics and a Regenstrief Institute affiliated scientist, directs CHPPR. Among his recent work are studies relating to physician malpractice, pharmaceutical industry influence in medical education, and physician support of health care financing reform.

**Ronald Ackermann, MD, MPH**, assistant professor of medicine and a Regenstrief Institute affiliated scientist, is the deputy director. His research has focused on the development and evaluation of “partnered” approaches for preventing and managing chronic health conditions, especially diabetes and physician support of national health insurance.

#### **IU RESEARCHERS LAUNCH SOCIAL NETWORKING AND RESEARCH MANAGEMENT TOOL FOR SCIENTISTS**

IU researchers recently launched Laboratree, a web-based solution to the complex problems of scientific collaboration. Designed to streamline research and enhance collaborative social networking for the science community, Laboratree will enable scientists to securely manage research papers and data, organize groups and projects, send group messages, author blogs, and customize personal and group profiles – all online.

IUSM informatics researchers have developed the Laboratree Research Management System to facilitate day-to-day research activities in a way that addresses the culture of scientific collaboration, eliminates barriers to entry, and uses the familiar structure of social networking to enable research.

“My thinking is that we should actually try to do things with a social network – that is, we should consider the social network the model by which we do things,” said **Sean Mooney, PhD**, assistant professor of medical and molecular genetics, who developed Laboratree with colleagues at the Center for Computational Biology and Bioinformatics.

In addition to professional social networking, collaborators can upload documents to Laboratree, where colleagues can



view, download, edit, and manage research papers and data. Colleagues will have access to all versions of a document, tracking edits made, while an intuitive check-in, check-out system eliminates conflicting changes.

Dr. Mooney said the system is still in development and people interested in learning about and testing the system are encouraged to register at <http://laboratree.org/>.

#### **NEWLY DISCOVERED MOLECULE PROMISES BETTER TREATMENTS FOR HEART ATTACKS, HEART SURGERY**

Scientists have discovered a compound that could lead to new treatments for heart attacks as well as methods to protect hearts during open heart surgery and other situations in which blood flow to the heart is interrupted.

In the process, the researchers uncovered cellular mechanisms that help explain how alcohol can protect against heart attack damage. In addition, they have uncovered a possible key to reducing chest pain and the heart attack damage among millions of people of East Asian descent who are genetical-

ly unable to respond to nitroglycerin and other cardiovascular treatments.

A research team of scientists at Stanford and Indiana universities schools of medicine reports in the Sept. 12 issue of the journal *Science* that by jump-starting a particular enzyme they were able to significantly reduce the amount of cell death caused by lack of blood flow to the heart.

The group found that administering a compound called Alda-1 activated the enzyme, reducing heart muscle damage in experiments involving rats. First, however, the researchers studied various mechanisms known to provide cardioprotection to heart muscle cells, including the use of ethanol, to better understand how those mechanisms worked. That work revealed a cellular signaling system that activated a particular enzyme called ALDH2.

“The idea was to find a small molecule that could bypass the signaling process and activate the enzyme directly,” said **Thomas D. Hurley, PhD**, professor of biochemistry and molecular biology and director of IU’s Center for Structural Biology.

Although still far from implementation, the benefit could extend to about 40 percent of people of East Asian descent who carry a mutated form of the ALDH2 enzyme, which puts them at increased risk of cardiovascular damage. ■

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**CME QUESTIONS**

- Which of the following is a core disturbance associated with PDDs?
  - Repetitive behavior
  - Impaired social interaction
  - Impaired communication
  - All of the above
- In the majority of cases, autism is associated with mental retardation.
  - True
  - False
- Which of the following behaviors or responses is commonly associated with autism?
  - Catatonia
  - Hyposensitivity (to sounds, tastes, smell, touch)
  - Demand for consistency
  - All of the above
- Which of the following statements about autism and Asperger's disorder is accurate?
  - Asperger's disorder is associated with normal IQ and language development
  - Intense preoccupation with a single topic is common in children with autism
  - At least half of all autism cases are linked to fragile X syndrome
  - All of the above
- What is first-line pharmacotherapy for irritability and dysfunctional behavior in children and adolescents with PDDs?
  - SSRIs
  - Atypical antipsychotics
  - Central nervous system stimulants
  - Mood stabilizers

**EVALUATION**

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