CURRENT CONCEPTS

Review Articles

CURRENT CONCEPTS

AUTISM

ISABELLE RAPIN, M.D.

FEW disorders seem more confusing than autism. Common stereotypes — of a severely withdrawn, mute child with ceaselessly repetitive activities and an averted gaze or a freakish-looking, inept, mathematical prodigy — do not accurately reflect the broad spectrum of autism. Far from being emotionally ill but otherwise normal, persons with autism are now considered to have one of a group of developmental disorders of brain function that have such a broad range of behavioral consequences and severity that they are referred to, collectively, as pervasive developmental disorder (often called PDD) in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Within the spectrum of pervasive developmental disorder, the narrower term “autistic disorder” is used to refer to classic autism.

SYMPTOMS OF AUTISM

Behavior

The main symptoms of autism are deficits in sociability, reciprocal verbal and nonverbal communication, and the range of the child's interests and activities. Contrary to popular view, children with autism may be affectionate, but on their terms and without the expected joy and reciprocity. Parents of such toddlers may describe them as independent rather than aloof and may be proud of their supposed self-sufficiency. The inordinate shyness, fearfulness, anxiety, or lability of mood of the child with autism may be replaced by detachment or depression in adolescence. Unprovoked aggressiveness, if not dealt with early, may become a major problem and lead to a need for heavy medication or institutionalization.

Communication

Although the lack of a drive to communicate or the withholding of speech has a role in all silent children, young children with autism have actual language disorders as well.

Play

Young children with autism do not know how to play. They may manipulate or line up toys without apparent awareness of what the toys represent, and they do not engage in pretend play, which, in nor-

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mal children, starts before the age of two. The ob-
servation of what a preschool child does with repre-
sentational toys is a sensitive and efficient way to
detect autistic traits.

Attention and Activities

Some children with autism have unusually long
attention spans during self-initiated activity, although they are virtually incapable of focusing on a
joint endeavor with another person. They often
have temper tantrums if someone tries to make them switch activities or if a ritual behavior is interrupted. An inability to concentrate, together with intrusive stereotypies such as hand flapping, may prevent children from engaging in meaningful activity or social interaction. A decreased need for sleep and frequent
awakenings during the night are particularly trou-
blesome for parents and care givers.

*The definitions are adapted from DSM-IV.

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**TABLE 1. THE SPECTRUM OF AUTISM (Pervasiv Developmental Disorder).**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autistic disorder</td>
<td>Classic autism involves severe qualitative deficits in all three of the following behavioral domains: Social interaction; Language, communication, and play; and Deficits manifested as stereotypes, perseveration, and a narrow range of interests and activities.</td>
</tr>
<tr>
<td>Asperger's syndrome</td>
<td>Is the disorder in nonretarded, often clumsy children without speech delay who have deficient sociability and a narrow range of interests.</td>
</tr>
<tr>
<td>“Pervasive developmental disorder not otherwise specified”</td>
<td>Is the disorder in children with autistic behavior who do not fulfill the criteria for any of the other disorders on the spectrum.</td>
</tr>
<tr>
<td>Disintegrative disorder (Heller's syndrome)</td>
<td>Is the disorder in previously completely normal children who undergo a massive regression between the ages of 2 and 10 years, resulting in severe acquired autism, usually with loss of cognitive skills. By definition, it does not occur in the context of a degenerative disease of the brain or schizophrenia.</td>
</tr>
<tr>
<td>Rett's disorder</td>
<td>Is a specific disorder limited to girls with acquired microcephaly, infantile regression, lack of hand use, striking stereotypic hand movements, severe retardation, and other neurologic problems.</td>
</tr>
</tbody>
</table>

*The table is adapted from DSM-IV.*

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**TABLE 2. CRITERIA FOR AUTISTIC DISORDER.**

A total of six or more manifestations from 1, 2, and 3 below:

1. Qualitative impairment of social interaction (at least two manifestations)
   a. Marked impairment in the use of multiple types of nonverbal behavior such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interactions;
   b. Failure to develop peer relationships appropriate to developmental level;
   c. Lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by lack of showing, bringing, or pointing out objects of interest); and
   d. Lack of social or emotional reciprocity.

2. Qualitative impairment of communication (at least one manifestation)
   a. Delay in, or lack of, development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gestures or mime);
   b. In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others;
   c. Stereotyped and repetitive use of language or idiosyncratic language; and
   d. Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level.

3. Restrictive and stereotyped patterns of behavior, interests, and activities (at least one behavioral manifestation)
   a. Encompassing preoccupation with one or more restricted, repetitive, and stereotyped patterns of interest that is abnormal either in intensity or focus;
   b. Apparently inflexible adherence to specific, nonfunctional routines or rituals;
   c. Stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements); and
   d. Persistent preoccupation with parts of objects.

Delays or abnormal functioning, with onset before the age of 3 years, in at least one of the following areas:
Social interaction;
Language as used in social communication; and
Symbolic or imaginative play.
A determination that Rett's disorder or childhood disintegrative disorder does not account better for the observed symptoms.

*The criteria are adapted from DSM-IV.*
Cognition

Approximately 75 percent of persons with autism are mentally retarded; their cognitive level is significantly associated with the severity of their autistic symptoms. Preschool IQ tests do not predict outcome reliably, because some children in effective treatment programs improve significantly. The results of neuropsychological testing typically reveal an uneven cognitive profile, with nonverbal skills generally superior to verbal skills (except in Asperger’s syndrome, in which the reverse pattern may exist). Poor insight into what others are thinking persists throughout life. Creativity is usually limited. A small minority of persons with autism have surprisingly good musical, mathematical, or visual–spatial abilities, despite profound deficits in other domains. In cases in which these abilities are astounding, patients with autism may be called savants (formerly idiot savants).

Sensorimotor Symptoms

The neurologic substrate of autistic deficits is unknown. In young children, common findings include increased joint laxity and hypotonia, clumsiness, apraxia, and toe walking. Motor stereotypies are often striking and, besides hand flapping, may include pacing, spinning, running in circles, twirling a string, tearing paper, drumming, and flipping light switches, as well as oral stereotypes like humming or incessant questioning. Self-injurious behavior such as biting, head banging, and gouging may be an extremely severe form of stereotypy, which current theory attributes to increased levels of endorphins. In relatively well-functioning adults, childhood stereotypes often persist in an unobtrusive miniaturized form, such as finger rubbing, that may pass unnoticed.

Children with autism may react paradoxically to particular sensory stimuli, being sometimes hypersensitive and sometimes oblivious to certain sounds, tactile stimuli, or pain. They may sniff their food and have an intense dislike of certain tastes or textures. Visual perception is usually superior to auditory perception. Such children may cover their ears and stare with fascination at some visual displays and have an outstanding rote visual or auditory memory.

EPILEPSY AND AUTISTIC REGRESSION

By adulthood, about a third of persons with autism will have had at least two unprovoked epileptic seizures. Autism may follow infantile spasms and Lennox–Gastaut syndrome, two malignant forms of epilepsy in early childhood, but all types of seizure may occur in autism. The probability of epilepsy increases throughout childhood with a peak in adolescence, and it is linked to mental retardation and motor deficits.

About a third of parents of children with autism report regression of their child’s language, social, and play skills, most often before the age of two, followed by a prolonged plateau and eventual improvement, but not full recovery. Some 10 percent of children given a diagnosis of autism are later found to have a paroxysmal electroencephalographic (EEG) pattern of the type seen in acquired epileptic aphasia (Landau–Kleffner syndrome), or electrical status epilepticus during slow-wave sleep (Table 4). This EEG pattern may be associated with the late, severe regression known as disintegrative disorder, which has a particularly poor prognosis. No one knows how often subclinical epilepsy is associated with autistic regression, because very few toddlers come to medical attention at the time of the regression, which occurs so early as to appear to be only a development-
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TABLE 4. CONDITIONS ASSOCIATED WITH BEHAVIORAL AND LANGUAGE REGRESSION WITH OR WITHOUT EPILEPSY.

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>DEFINITION AND RELATION TO EPILEPSY</th>
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<tbody>
<tr>
<td>Autistic regression6</td>
<td>Sudden or insidious regression (or prolonged plateau) in the development of language, sociability, play, and often cognition, in some cases with fluctuations, usually followed by improvement but not full recovery. Infrequently associated with clinical seizures. Prevalence of contemporaneous subclinical epileptiform EEG activity unknown; later prevalence is on the order of 10 to 20 percent.</td>
</tr>
<tr>
<td>Peak age: 18 to 24 months</td>
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<tr>
<td>Duration: regression lasts weeks, months, or several years; recovery is virtually always incomplete</td>
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</tr>
<tr>
<td>Disintegrative disorder3,4</td>
<td>Insidious or sudden severe autistic regression (in language, behavior, motor skills, and usually cognition) after entirely normal early development, including the ability to speak communicatively in sentences. Associated in some cases with seizures or an epileptiform EEG, including electrical status epilepticus in slow-wave sleep. Cause almost certainly heterogeneous.</td>
</tr>
<tr>
<td>Peak age: 2½ to 3 years (range, 2 to 10 [perhaps later])</td>
<td></td>
</tr>
<tr>
<td>Duration: regression persists for weeks, months, or years; recovery is usually incomplete, with severe permanent sequelae</td>
<td></td>
</tr>
<tr>
<td>Acquired epileptic aphasia (Landau–Kleffner syndrome)9</td>
<td>Regression in language development, associated with clinical seizures or a frankly epileptiform EEG enhanced in sleep, in a child with previously entirely normal language. Usually affects language comprehension, often to the point of verbal auditory agnosia, with resultant severely impaired expression. Rarely, affects expression selectively. Seizures respond to anticonvulsants; language deficit may or may not respond and be permanent.</td>
</tr>
<tr>
<td>Peak age: 5 to 7 years (range, 1 to 10)</td>
<td></td>
</tr>
<tr>
<td>Duration: weeks, months, or several years for seizures and EEG abnormalities; variable for language deficit</td>
<td></td>
</tr>
<tr>
<td>Electrical status epilepticus during slow-wave sleep (or continuous spikes and waves during slow-wave sleep)33</td>
<td>EEG diagnosis with or without clinical seizures; often but not invariably associated with severe autistic regression affecting language, behavior, and cognition, amounting to disintegrative disorder. Recovery rarely complete; deficits often permanent.</td>
</tr>
<tr>
<td>Peak age: 4 to 5 years (range, up to 12)</td>
<td></td>
</tr>
<tr>
<td>Duration: weeks, months, or years</td>
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</tr>
</tbody>
</table>

...tial fluctuation of no clinical significance. There is an urgent need to study infants at the time of the regression, since the administration of anticonvulsants or steroid hormones might be able to arrest the regression and the associated seizures or subclinical epilepsy.

PREVALENCE

Autism was once thought to be very rare. Studies in several countries that sought to identify children with autism through a canvass of hospitals, clinics, physicians, special schools, and other institutions found a prevalence of about 4 children with autism per 10,000 children in the general population.\(^9,38\) The advent of explicit behavioral criteria in DSM-IV and the International Classification of Diseases\(^9,10,38\) has resulted in the identification of many less severely affected children and adults; early estimates of prevalence were therefore probably too low. A complete survey of 21,610 Japanese children, followed from birth to three years of age, found 1.3 children with autistic disorder per 1000 and another 0.7 per 1000 with autistic traits.\(^32\) A questionnaire survey of all 20,800 children 6 to 14 years of age in Nova Scotia found a prevalence of 1 per 1000.\(^33\) These figures are similar to the prevalence of 1 to 2 per 1000 found among children 3 to 17 years of age in southern Sweden (in addition to approximately 3 per 1000 school-age children who have Asperger’s syndrome).\(^9\) Autistic features were found in a much higher proportion of mentally retarded children (20 percent).\(^9\) These more recent, higher estimates suggest that in the United States there are at least 58,000, and perhaps as many as 115,000, children with autism among the 57.6 million children 1 to 15 years of age. There are no reliable figures on the prevalence of autism among adults.

CAUSES

Autism has many defined biologic causes, none of them unique to autism.\(^9,10,34\) Some prenatal factors include intrauterine rubella; tuberous sclerosis; disorders such as Cornelia de Lange’s syndrome; chromosomal abnormalities, such as fragile X, Angelman’s syndrome, and even, occasionally, Down’s syndrome; as well as brain abnormalities such as hydrocephalus. Perinatal difficulties have little causative role in autism.\(^35\) Frequently cited postnatal conditions associated with autism are untreated phenylketonuria, infantile spasms, herpes simplex encephalitis, and very rarely, a focal brain lesion such as a neoplasm or some other rare disease or syndrome.\(^36\) Estimates of the proportion of all cases of autism associated with or attributable to these various factors depend on diagnostic criteria, the extent of medical evaluation, and the definition of risk factors. These estimates vary from about 10 percent\(^37\) to over 30 percent.\(^9,34\)

Evidence that genetics is an important, but not exclusive, cause of so-called primary autism (i.e., autism with no associated neurologic condition) includes a 3 to 8 percent risk of recurrence in families with one affected child. Other evidence is provided by the existence,\(^38,39\) especially among families with children with Asperger’s syndrome, of an affected parent. In studies of twins, there is a concordance of...
over 90 percent for the diagnosis, if not the severity, of autism among monozygotic twins, and a concordance of 5 to 10 percent among same-sex dizygotic twins. A strong concordance, with different levels of phenotypic severity, suggests that the expression of one or more genes interacts with nongenetic factors. DeLong has reported a familial linkage of autism to affective disorders and Comings and Comings a link to Tourette's syndrome. Thus far, no specific gene for autism has been identified, although a possible link to the serotonin-transporter gene has recently been suggested.

THE NEUROLOGIC BASIS OF AUTISM

The existence of a large literature describing a wide variety of neural abnormalities in autism has led to much speculation about the disease. However, neither a coherent anatomical nor pathophysiological theory of autism nor a biologic diagnostic test has yet been developed.

Neuropathological studies of fewer than 35 brains of patients with autism are available; none were done with state-of-the-art methods. Preliminary findings from these studies include a paucity of Purkinje cells and granular cells in parts of the cerebellar cortex and smaller than normal, more tightly packed cells in some cerebellar nuclei and limbic structures, including the amygdala and hippocampus, suggesting prenatal dysgenesis. On average, the studied brains tend to be large.

Routine imaging of the brain is usually unrevealing in primary autism. Various morphometric studies have found hypoplasia of parts of the cerebellar vermis, thinness of the brain stem and the posterior corpus callosum, and mild widening of the parietal sulci and ventricles in some, but by no means all, brains. Single-photon-emission computed tomography and positron-emission tomography have not yet revealed a coherent pattern of functional deficits, although bitemporal hypometabolism may be present in autism after infantile spasms.

EEGs are helpful when they reveal frankly epileptiform activity. Brain-stem auditory evoked potentials are normal in the absence of hearing loss or diffuse brain damage. Evidence of delays in the early negative components of auditory event-related potentials and abnormalities in late components associated with word classification supports the idea that there is aberrant processing of auditory language skills in autism.

Guided in part by empirical neuropharmacologic studies, neurochemical research on autism has focused on neurotransmitters and neuromodulators, first, the mesolimbic dopamine system; then, endogenous opioid systems and oxytocin; and, in current research, serotonin, examined because of an identified link between autism and affective disorders and the discovery of some favorable behavioral effects of serotonergic drugs. As in other neurologic evidence, there are a large variety of reported abnormalities but no unifying theory or explanation.

COURSE AND PROGNOSIS

Autism tends to improve, in some cases substantially, as children start to acquire language and learn to use it to communicate needs and to influence other people. If behavior deteriorates in adolescence, it may reflect the effects of hormonal changes, the difficulty of meeting greater behavioral demands in an increasingly complex social milieu, or perhaps depression. Although most patients with autism will remain dependent to some degree as adults, those with adequate social skills may find a specialized niche that enables them to become self-supporting. As a greater number of mildly affected people are identified, we may find that the proportion of those who achieve independence has been underestimated. Social skills rarely improve enough, however, to permit successful marriage, although mildly affected persons with autism occasionally do marry and have children.

DIAGNOSIS

Correct diagnosis depends on an accurate developmental history focused on types of behavior typical of autism and on the evaluation of current functional skills. Cognitive and behavioral evaluation should include an assessment of sociability (an interest in persons rather than objects and the ability to engage joyfully in an activity initiated by someone else and, in young children, in imaginative play with representational toys), language (comprehension, production and conversational use of speech, and voice quality), and the patient’s choice of activities (including the presence of stereotypic and pointless activities). The use of the DSM-IV and any of the several autism-specific diagnostic inventories substantially increases diagnostic reliability.

In the absence of evidence of a specific underlying medical disorder, investigations such as batteries of metabolic tests produce little helpful information. Routine chromosome studies also provide little useful data, but they are reasonable to undertake if the parents of the patient are a young couple who want further children. Probably less than 5 percent of children with autistic traits have fragile X or any of the other, rarer chromosomal abnormalities.

Children with autism typically have normal, or somewhat large, head circumferences. Clinical imaging studies are not very useful unless the neurologic examination suggests a possible structural lesion. EEGs are indicated for children in whom epilepsy is suspected, but it should be kept in mind that nonepileptic staring spells are much more common than absence seizures. A prolonged sleep EEG that includes study of stage III and IV sleep is recom-
mended for children without seizures who have regressed or who have fluctuating deficits and for mute or poorly intelligible children who may have verbal auditory agnosia.6,24 The value of administering valproate or corticosteroids to a child without seizures who has regressed and has a frankly epileptiform EEG is uncertain.

INTERVENTION

No drug or other treatment cures autism, and many patients do not require medication. However, psychotropic drugs that target specific symptoms may help substantially (Table 5). The effectiveness of methylphenidate in improving attention capacity can be assessed rapidly because of the very short half-life of the drug. With other psychotropic agents, an initial small dose of a single agent should be given; the dosage should be increased sufficiently slowly to gauge effectiveness before any switching of drugs. Serotonergic antidepressants are often prescribed to control stereotypies, perseveration, and mood swings, but controlled trials of these drugs in autism are needed. In view of the potential need for their long-term use, especially to control aggression, medications must not have sedative effects or produce irreversible side effects such as tardive dyskinesia.

The most important intervention in autism is early and intensive remedial education that addresses both behavioral and communication disorders.60 The effective approaches use a highly structured environment with intensive individual instruction and a high teacher-to-student ratio.60,61,62 Occupational and physical therapy should address specific deficits. Parents need specific instruction in how to deal with tantrums and destructive behavior and in useful techniques for keeping their children organized and occupied so as to minimize detrimental effects on the family. Parents require ongoing counseling and support. They must understand that they are not responsible for their child’s condition. Desperate parents may need explicit counseling about the questionable value of unconventional, and often expensive, dietary, medical, and other therapies that, despite being without proved efficacy, are widely used.61 Parents must be given information about appropriate schools, respite facilities, parent groups, and other community-based support systems. Adolescents and adults often require assistance in securing meaningful work and living arrangements in group homes when their families are no longer able to provide shelter. Patients capable of living independently may need help in finding an appropriate and supportive school and job. One hopes that in the future only a minority of adults with autism will live out empty lives in institutions.

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**TABLE 5. Medications Used in Patients with Autism.**

<table>
<thead>
<tr>
<th>Type of Drug</th>
<th>Examples</th>
<th>Indications</th>
<th>Principal Undesirable Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulants</td>
<td>Methylphenidate, pemoline</td>
<td>Attention deficit–hyperactivity</td>
<td>Irritability, aggressiveness, stereotypies, tics, sleeplessness; in rare cases, hepatotoxicity of pemoline</td>
</tr>
<tr>
<td>Noradrenergic agents (beta-blockers and α₂ agonists)</td>
<td>Propranolol, clonidine (e.g., patch)</td>
<td>Explosive behavior, aggressiveness</td>
<td>Depression, nightmares, sleepiness, hypotension, dry mouth</td>
</tr>
<tr>
<td>Serotonin-reuptake inhibitors and agonists, antidepressants</td>
<td>Fluoxetine, clomipramine, sertraline, fluvoxamine</td>
<td>Perseveration, obsessions, rigidity, aggressiveness, depression</td>
<td>Dry mouth, sleep disturbances, constipation, agitation, restlessness</td>
</tr>
<tr>
<td>Dopamine-receptor blockers</td>
<td>Haloperidol, thioridazine, chlorpromazine, pimozide</td>
<td>Aggressiveness, destructiveness, self-injury</td>
<td>Sedation, affective blunting, dystonia, parkinsonism, tardive and withdrawal dyskinesias</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>Buspirone</td>
<td>Anxiety</td>
<td>Sedation, restlessness (rarely), gastrointestinal symptoms</td>
</tr>
<tr>
<td>Opioid antagonists</td>
<td>Naltrexone</td>
<td>Self-injury, stereotypy</td>
<td>Long-term effects unknown</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>Lithium, valproate, carbamazepine</td>
<td>Mood lability, aggressiveness</td>
<td>Tremor, weakness, need to monitor blood levels</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Valproate, carbamazepine, lamotrigine, vigabatrin</td>
<td>Epilepsy; possibly autistic regression with epileptiform EEG (including electrical status epilepticus in slow-wave sleep) without clinical seizures</td>
<td>Drowsiness, ataxia, rashes; hyperphagia and tremor with valproate</td>
</tr>
<tr>
<td>Hormones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep aids</td>
<td>Melatonin</td>
<td>Sleep disturbances</td>
<td>Long-term effects unknown</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Corticotropin, prednisone</td>
<td>Possibly autistic regression with epileptiform EEG (including electrical status epilepticus in slow-wave sleep) without clinical seizures</td>
<td>Obesity, hypertension, infections, psychosis</td>
</tr>
</tbody>
</table>

*Data are from Cohen and Volkmar.10
CURRENT CONCEPTS

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REFERENCES