Intellectual Disabilities

Oscar Purugganan, MD, MPH*

*Department of Pediatrics, Columbia University Medical Center, New York, NY

Education Gaps

1. Pediatricians must have knowledge of the diagnostic criteria and levels of severity of intellectual disability (ID).
2. Pediatricians should be informed about current developments in the evaluation of a child with ID.
3. Pediatricians must be familiar with treatment and resources for children with ID.

Objectives

After completing this article, readers should be able to:

1. Formulate a plan for the evaluation of children with intellectual disability (ID) both in terms of coming to a diagnosis (evaluation of cognitive and adaptive skills) and performing a diagnostic evaluation.
2. Formulate treatment options and referral for services for children with ID.

Intellectual disability (ID) is a neurodevelopmental disorder that is characterized by deficits in both intellectual functioning and adaptive functioning, whose onset is in the developmental period. (1) It affects approximately 1% to 3% of the population. (2) Intellectual disability has replaced the former term, mental retardation, through a federal statute (Rosa’s Law, Public Law 111-256). Global developmental delay (GDD) is the term used to describe children aged 0 to 5 years with significant delays in 2 or more areas of development. (1) Although these delays may be transient, it is estimated that approximately two-thirds of children diagnosed as having GDD would eventually carry the diagnosis of ID after 5 years of age. (3)

As part of routine health-care visits, the American Academy of Pediatrics (AAP) recommends developmental surveillance at every well-child visit and formal developmental screening at ages 9, 18, and 24 or 30 months. (4) Screening instruments such as the Ages and Stages Questionnaire, the Pediatric Evaluation of Developmental Skills, and the Denver Developmental Screening Test-II help to identify children who will require more formal developmental assessments, where a child’s developmental skills are more thoroughly evaluated and that will likely include testing of cognitive abilities.

AUTHOR DISCLOSURE Dr Purugganan has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AAIDD American Association of Intellectual and Developmental Disabilities
AAP American Academy of Pediatrics
CDC Centers for Disease Control and Prevention
CT computed tomographic
DSM Diagnostic and Statistical Manual of Mental Disorders
GDD global developmental delay
ID intellectual disability
IEP Individualized Education Program
MRI magnetic resonance imaging
WISC-V Wechsler Intelligence Scale in Children-V
WPPSI-IV Wechsler Preschool and Primary Scale of Intelligence-IV
PRESENTATION

Intellectual disability may present in various ways and at different ages in the pediatric patient. The more severe the impairment, the more likely ID is to present and be diagnosed earlier. Correspondingly, the milder the impairment, the more likely it is to manifest at an older age. It is possible that milder forms of ID may go unrecognized until the school-age years. A child with ID may present initially with receptive and expressive language delays, adaptive skills delays (eg, toileting, dressing), fine motor deficits, difficulties in problem-solving skills, social immaturity, and behavioral difficulties. It is important to consider that intelligence/developmental tests during the first 3 years of life involve many sensorimotor tasks that may affect the accurate measurement of the cognitive level of a child with a motor problem (eg, cerebral palsy, hypotonia) or sensory impairment (visual and auditory). Among the different areas of development monitored in early childhood (language, problem-solving, gross/fine motor, personal-social skills), gross motor skills are the least correlated with ID.

ASSESSMENT

Assessment of Intellectual Functioning

Intellectual functioning is measured by standardized instruments such as the Wechsler Intelligence Scale in Children-V (WISC-V), the Wechsler Preschool and Primary Scale of Intelligence-IV (WPPSI-IV), and the Stanford-Binet Intelligence Scales-V. These are generally performed by a certified psychologist or special educator. These instruments are designed to measure a child’s general intellectual ability and include verbal and nonverbal subtests. Persons with ID exhibit deficits in both verbal and nonverbal domains, although not necessarily to the same degree. An overall full-scale IQ score is derived from the combination of verbal and nonverbal IQ scores.

The WISC-V and WPPSI-IV include the following indices: verbal comprehension index, visuospatial index, fluid reasoning, working memory, and processing speed. The Stanford-Binet subtests include knowledge, quantitative reasoning, visuospatial reasoning, working memory, and fluid reasoning. These instruments can be administered in children as early as approximately age 2 years (Stanford Binet-V) to 2½ years (WPPSI-IV), although it is important to note that intelligence scores become more stable after 5 years of age. (5)(6)(7) People with intelligence scores more than 2 SD below the mean are considered to fall in the ID range. Using the normal curve to delineate levels of intelligence with a mean IQ score of 100 and a standard deviation of 15, it is estimated that approximately 2.5% of the population would fall in the ID range with IQ scores less than 70 (2 SD below the mean). Those with IQ scores of 70 to 84 are considered to have borderline intelligence. In school, children with borderline intelligence may be considered “slow learners” but not to the same degree as children with ID. Making a diagnosis of ID is not always straightforward; it may require a few visits to fully assess a child, and ongoing follow-up may be necessary.

Assessment of Adaptive Functioning

Adaptive functioning is measured through questionnaires such as the Vineland Adaptive Behavior Scales and the Adaptive Behavior Assessment System, (5) which are administered by certified clinicians such as psychologists or social workers with information obtained from the patient’s primary caregivers. In the Diagnostic and Statistical Manual of Mental Disorders (DSM), Fifth Edition, adaptive functioning is operationalized in terms of 3 domains: the conceptual domain (eg, competence in memory, language, academics, judgment), the social domain (eg, social awareness, interpersonal communication skills, friendships), and the practical domain (eg, learning and self-management). Impairment in at least 1 of these domains, wherein ongoing support is needed, should be present to meet the definition of ID. (1)

The American Association of Intellectual and Developmental Disabilities (AAIDD), the oldest interdisciplinary professional organization that has been instrumental in the definition and recognition of ID and its earlier iterations, uses a similar definition of ID as the DSM-V. The AAIDD defines ID as a disability characterized by “significant limitations in both intellectual functioning and adaptive behavior” with the onset of deficits before 18 years of age. (8)

LEVELS OF SEVERITY

The DSM-V and the AAIDD characterize the severity of ID based on a person’s adaptive functioning and the amount of support a person needs. These are described and summarized in the following subsections (Table 1). (1)(6)

Mild ID

A person with mild ID may manifest difficulties in late preschool or the early school-age years. They may have difficulties in the academic setting (early reading, writing, arithmetic, time, and money) and seem more socially immature compared with other children their age. Communication and thinking may be more concrete and less mature than that of their peers. Although they may function
appropriately in matters of personal care and many even eventually live independently, they may need support intermittently, particularly in complex daily living situations. Some may be able to reach a sixth-grade level in academic functioning.

**Moderate ID**

A person with moderate ID generally presents earlier than those with mild ID, manifesting with learning and language difficulties in the preschool years and deficits in social and communication behavior, which require limited although possibly substantial support. Those affected may ultimately be able to perform basic tasks for personal care (eg, dress, toilet, and eat independently), but significant amounts of support time and teaching may be needed. During adulthood, they may be employed in jobs that require minimal communication and cognitive skills and may be able to participate in all household tasks but with ongoing support and teaching. Some may be able to reach a second-grade level in academic functioning.

**Severe ID**

A person with severe ID has limited capacity to understand written language and the concepts of numbers and time and would need extensive support from caretakers throughout life. Spoken language is also very limited, and they may have limited understanding of speech/language and gestural communication. Children with severe ID would require extensive support and supervision for all activities of daily living. Some may reach the pre-K level in academic functioning.

**Profound ID**

A person with profound ID has conceptual skills that do not go beyond the concrete, and ability mainly involves manipulation of objects, at best. They have very limited understanding of symbolic language, although they may be able to understand basic instructions. A person with profound ID requires pervasive support and is dependent in all aspects of personal care and daily living.

In the *DSM-IV* and *DSM-IV-TR*, the previous editions of the *DSM*, (9) levels of ID were extrapolated by increasing standard deviations from the mean IQ; thus, mild ID was defined as IQ scores between 2 and 3 SD below the mean of 100 (IQ scores from 50–55 to approximately 70); moderate ID corresponded to IQ scores between 3 and 4 SD below 100 (IQ scores from 35–40 to 50–55); severe ID was defined as IQ scores between 20 to 25 and 35 to 40; and profound ID corresponded to IQ scores less than 20 to 25. Although this classification may still be useful, using IQ scores solely does not accurately and completely reflect how well an individual is able to function, hence the shift in the classification of the levels of ID based on the individual’s level of adaptive function.

**ETIOLOGY**

There are many different etiologies for ID: genetic disorders (eg, chromosomal disorders, including X chromosome disorders, contiguous gene deletions, and single-gene disorders), environmental causes (eg, alcohol and other teratogens, prenatal infections), traumatic brain injury, neurologic/brain disorders, nutritional deficiencies, and inborn errors of metabolism. A significant number of people with ID have no identifiable cause (Table 2). It is more likely to identify a biological cause in more significant forms of ID (such as moderate, severe, and profound ID) than in mild ID, which may be influenced by cultural, linguistic, and societal difficulties. (5)

**Genetic Causes of ID**

Online Mendelian Inheritance in Man (10) lists approximately 800 genetic syndromes associated with ID. These syndromes may have X-linked, autosomal dominant, or

<table>
<thead>
<tr>
<th>LEVEL OF ID (% CHILDREN WITH ID)</th>
<th>LEVEL OF SUPPORT (IN CONCEPTUAL, SOCIAL, PRACTICAL DOMAINS)</th>
<th>ASSOCIATED ESTIMATED IQ SCORE</th>
<th>PROJECTED ULTIMATE ACADEMIC ACHIEVEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (85%)</td>
<td>Intermittent</td>
<td>55–70</td>
<td>Up to sixth-grade level</td>
</tr>
<tr>
<td>Moderate (10%)</td>
<td>Limited</td>
<td>40–55</td>
<td>Up to second-grade level</td>
</tr>
<tr>
<td>Severe (3%–4%)</td>
<td>Extensive</td>
<td>25–40</td>
<td>Preschool level</td>
</tr>
<tr>
<td>Profound (1%–2%)</td>
<td>Pervasive</td>
<td>&lt;25</td>
<td>–</td>
</tr>
</tbody>
</table>

Note: The level of severity is based on the level of adaptive functioning and support. (1)(6)
autosomal recessive inheritance. Medical evaluation for those with syndromic forms of ID will be based on known clinical manifestations of the genetic syndrome. (10)(11)(12) Table 3 summarizes some of the more common genetic syndromes associated with ID.

Down syndrome is the most common genetic cause of ID, with prevalence of 1 in 800, with 95% of cases due to trisomy 21, 4% to 5% due to an unbalanced translocation between chromosome 21 and another chromosome (usually chromosome 14), and 1% attributed to mosaicism. The clinical phenotype is very well-known and includes a distinct facies, congenital heart disease, hypothyroidism, gastrointestinal disorders, and hypotonia. Intelligence is usually in the mildly-moderate range of ID, with verbal skills weaker than nonverbal skills. It is also associated with early Alzheimer disease and depression. The AAP has published health maintenance guidelines for children with Down syndrome. (13)

Fragile X syndrome is a trinucleotide repeat disorder (CGG) and is the most common inherited cause of ID, affecting 1 in 4,000 individuals. Although it is much more common in males, fragile X syndrome may be diagnosed in girls as well. Fully affected males (with triplet repeats >200) manifest with significant ID as well as clinical features that may include relative macrocephaly, prominent ears, hypertelorism, and large testes in postpubertal individuals. Females with fragile X syndrome may present with milder forms of cognitive impairment. Fragile X syndrome also has a well-recognized association with autism spectrum disorders. (2)

Rett syndrome is due to a mutation of the MECP2 gene found in the X chromosome. It is primarily seen in girls (although it has also been identified in boys), where the clinical presentation includes a deceleration in the rate of head growth during the second year of life, hand-wringing and handwashing movements, language deficits/regression, and ID. It is more likely that males with MECP2 mutations present with neonatal encephalopathy than with GDD/ID. (2)

Certain contiguous gene disorders are also associated with ID. (10)(11)(12) Williams syndrome is caused by a deletion in chromosome 7q11 and presents with elfinlike facial features, mild to moderate ID (with nonverbal function being a significant weakness), and cardiac and renal manifestations. Angelman and Prader-Willi syndromes are a result of genetic imprinting, where clinical manifestations depend on which parent contributes to the deletion in chromosome 15q11.2-q13. Less commonly, these syndromes can also be attributed to uniparental disomy (2 copies of a chromosome from the same parent). Angelman syndrome is due to a maternally derived deletion (or paternal disomy) and is associated with severe-profound ID, microcephaly, and hand movements, whereas Prader-Willi syndrome is caused by a deletion in the paternally derived chromosome (or maternal disomy). The clinical course of patients with Prader-Willi syndrome is unique and consists of hypotonia and feeding difficulties in the neonatal period and obesity, atypical facial features, some degree of ID (low average to moderate ID), and psychiatric conditions (eg, obsessive compulsive disorder, skin picking) starting in toddlerhood or the preschool years. Smith-Magenis syndrome is caused by a deletion in the short arm of chromosome 17 (17p11.2) and is characterized by facial features such as midface hypoplasia and a broad nasal bridge, short stature, medical conditions such as visual problems, peripheral neuropathy, mild-moderate ID, sleep disturbances, and stereotypic and self-injurious behaviors. Miller-Dieker syndrome is due to a deletion in chromosome 17 and is associated with significant ID, microcephaly, and lissencephaly, where the brain is small and smooth due to a paucity of gyri and sulci.

Single-gene deletions associated with ID, aside from fragile X syndrome and Rett syndrome, include Rubinstein-Taybi syndrome (ID, short stature, microcephaly, abnormalities of the thumbs and toes) and tuberous sclerosis (skin manifestations, ID, autism, seizures, particularly infantile spasms). (10)(11)(12)

Environmental Causes of ID

Environmental causes of ID may also present with a set of symptoms that compose a syndrome. Fetal alcohol spectrum disorder results from prenatal exposure to alcohol and

---

**TABLE 2. Causes of Intellectual Disability**

<table>
<thead>
<tr>
<th>Genetic syndromes</th>
<th>Environmental causes</th>
<th>Nutritional (eg, severe malnutrition, chronic iron deficiency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal disorders, eg, Down syndrome</td>
<td>Alcohol and other teratogens</td>
<td></td>
</tr>
<tr>
<td>Contiguous gene deletions, eg, Williams syndrome</td>
<td>Prenatal infections</td>
<td></td>
</tr>
<tr>
<td>Single-gene deletions, eg, fragile X syndrome, Rett syndrome</td>
<td>Early childhood central nervous system infections</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Traumatic brain injury</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Central nervous system disorders/malformations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inborn errors of metabolism</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nutritional (eg, severe malnutrition, chronic iron deficiency)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not known</td>
</tr>
</tbody>
</table>
is characterized by alcohol-related birth defects, microcephaly and growth retardation, facial features such as short palpebral fissures, thin upper lip, smooth philtrum, neurocognitive problems such as ID and ADHD, and behavioral difficulties. (14) Intrauterine infections (TORCH) may present with developmental disabilities, growth defects, retinopathy, intracranial calcifications, and abnormalities in head size such as microcephaly (eg, cytomegalovirus) or macrocephaly (eg, toxoplasmosis associated with hydrocephalus). Most recently, congenital Zika infection has been implicated in causing significant microcephaly and other brain abnormalities in infants, which may likely lead to ID. (15)

Significant hypoxic-ischemic injury in the neonate may present early on with significant GDDs, motor impairment such as muscle hypertonicity/spasticity, microcephaly or poor head growth, and seizures. Many children with severe hypoxic-ischemic encephalopathy will eventually be diagnosed as having ID as well as cerebral palsy. Prematurity, especially for children with younger gestational age and more complicated courses, also places a child at risk for intellectual impairment and developmental disorders. (16)

In the United States, there has been a significant decrease in the levels of environmental lead due to successful public health efforts implemented during the past few decades. Consequently, there has been a dramatic decrease in blood lead levels in children. Mildly elevated lead levels are still detected, and these have been shown to be associated with mild cognitive delays. Lead toxicity has been associated with a decline of 1 to 2 IQ points (measured at 5 years or older) for every 10-point increase in lead level (17)(18) and a decrease of more than 7 IQ points for the first 10 mg/dL. (19) The AAP recommends further research to look more closely into these associations, through studies where confounders such as socioeconomic factors are better controlled for. (17)

Through newborn screening, conditions that may have led to ID if left untreated are being identified. These conditions include phenylketonuria and congenital hypothyroidism. In 2006, the American College of Medical Genetics Newborn Screening Expert Group recommended that 29 treatable conditions be universally screened in the newborn. (20) There are variations in each state as to the complete set of disorders that are being tested for. Pediatricians should be familiar with the conditions that are tested for in their state and ensure that each newborn undergoes the state’s newborn screening. The AAP has provided recommendations for pediatricians and medical homes as newborn screening has expanded. (21)

**APPRAOCH TO EVALUATION**

The approach to the evaluation for the etiology of the ID includes a thorough history, focused physical and neurologic

---

**TABLE 3. Common Genetic Syndromes Associated with Intellectual Disability (ID)**

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>GENETIC ABNORMALITY</th>
<th>DEVELOPMENTAL PROFILE</th>
<th>COMMON PHYSICAL FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down</td>
<td>Trisomy 21 (95%)</td>
<td>Mild to moderate ID</td>
<td>Down facies</td>
</tr>
<tr>
<td></td>
<td>Translocation (4%)</td>
<td>(Verbal - low)</td>
<td>Congenital heart disease</td>
</tr>
<tr>
<td></td>
<td>Mosaicism (1%)</td>
<td>Hypotonia</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Early Alzheimer disease</td>
<td>Gastrointestinal abnormalities</td>
</tr>
<tr>
<td>Fragile X</td>
<td>CGG trinucleotide repeat (&gt;200)</td>
<td>ID (typically moderate)</td>
<td>Elongated face</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Learning disorders</td>
<td>Macrocerephaly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autism spectrum disorder</td>
<td>Prominent ears</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperextensible joints</td>
</tr>
<tr>
<td>Rett</td>
<td>MECP2 deletion</td>
<td>ID</td>
<td>Enlarged testes (postpuberty)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stereotypic hand manerisms</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Language regression</td>
<td></td>
</tr>
<tr>
<td>Williams</td>
<td>7q11 deletion</td>
<td>Mild to moderate ID</td>
<td>Elfinlike facial features</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(nonverbal - low)</td>
<td>Cardiac (eg, supravalvular aortic stenosis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Renal abnormalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td>Angelman</td>
<td>Maternally derived deletion 15q (or paternal disomy)</td>
<td>Severe to profound ID</td>
<td>Microcephaly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atypical hand manerisms</td>
<td>Prognathism</td>
</tr>
<tr>
<td>Prader-Willi</td>
<td>Paternally derived deletion 15q (or paternal disomy)</td>
<td>ID (variable levels)</td>
<td>Neonate: hypotonia/feeding difficulties</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psychiatric conditions</td>
<td>Toddler: obesity, excessive appetite</td>
</tr>
</tbody>
</table>

---

Vol. 39 No. 6   JUNE 2018   303
examinations, and appropriate laboratory testing as warranted. (2)(7) History and physical examination together can identify the etiology in approximately 77% to 34% of cases of developmental delay. (7) Based on the history and physical examination findings, initial evaluation, including laboratory testing, genetic testing, and imaging, is determined.

History
The medical history includes a child’s current developmental functioning and a chronology of attainment of developmental milestones, a history of educational interventions, and a detailed prenatal/perinatal/neonatal history, which should include any history of maternal medical conditions and outcomes of previous pregnancies, maternal infections, medication intake and substance use/abuse, and a review of the newborn metabolic and hearing screens. A 3-generation family history of developmental problems; ID; learning deficits; neurologic, metabolic, or genetic conditions; and consanguinity should be explored. The child’s medical history should include any previous head injuries, central nervous system infections (such as meningitis or encephalitis), seizures and other neurologic conditions, and regression in skills.

Physical and Neurologic Examination
The physical examination focuses on growth parameters (especially head circumference), a thorough skin examination looking for lesions that may signify a neurocutaneous syndrome, a full neurologic examination, and evaluation for dysmorphic features that may suggest a genetic syndrome.

Evaluation of Head Size. Microcephaly, or a head circumference less than the third percentile for age, is highly associated with ID and is a manifestation of many disorders. Macrocephaly or a head circumference greater than the 97th percentile for age is associated with ID in the setting of certain genetic syndromes, such as fragile X syndrome and Sotos syndrome, as well as in patients with hydrocephalus. Autism spectrum disorder has also been associated with any previous head injuries, central nervous system infections (such as meningitis or encephalitis), seizures and other neurologic conditions, and regression in skills.

Evaluation of the Skin. Neurocutaneous syndromes may also be associated with ID. (10)(11) Tuberous sclerosis is associated with skin findings such as ash leaf spots (hypopigmented macules), shagreen patches (“peau d’orange”—textured skin lesions), and facial angiofibromas. Neurofibromatosis, which is associated with attention-deficit/hyperactivity disorder, learning disorders, and, less commonly, ID, is characterized by café au lait spots, inguinal and axillary freckling, Lisch nodules on eye examinations, and neurofibromas in the body.

Dysmorphic Features. The clinician should take note of dysmorphic features and atypical features that may be manifestations of certain genetic syndromes as described previously.

LABORATORY EVALUATION

Evaluation of Syndromic Forms of ID
If the clinician suspects a specific syndrome as an etiology for the ID/GDD, laboratory tests to confirm or rule out this syndrome should be performed. This may include chromosome analysis for Down syndrome and fluorescence in situ hybridization testing when specific genetic disorders are suspected, such as Prader-Willi/Angelman syndrome, Smith-Magenis syndrome, Williams syndrome, 22q11 deletion, Miller-Dieker syndrome, cri du chat syndrome, and Wolf-Hirschhorn syndrome.

For patients with suspected TORCH and Zika infections, serologic testing, neuroimaging, eye examination, and hearing tests are recommended. (23) A referral to a genetics specialist may be considered for further evaluation of dysmorphic features.

Evaluation of Nonsyndromic ID of Unknown Etiology
The American Academy of Neurology has released reports with recommendations for the evaluation of nonsyndromic GDD/ID of unknown etiology. (7)(24) It is widely regarded among clinical geneticists that chromosomal microarray analysis, with a yield of approximately 15% to 20%. (25) should be the first-line cytogenetic test for these cases. There has been less universal consensus for fragile X testing, but many experts recommend fragile X testing in boys and girls with ID who have clinical features of fragile X syndrome (macrocephaly, prominent ears, hyperextensible joints, perseverative speech, enlarged testes in pubertal boys), as well as unexplained GDD/ID (in both sexes) if there is a family history of ID. Many geneticists also recommend fragile X testing for unexplained ID if the microarray result is normal. Karyotyping is recommended if there is a suspicion of aneuploidy (presence of an abnormal number of chromosomes in a cell) such as Down syndrome, a history of many miscarriages, or a family history of chromosomal abnormalities. Some clinicians recommend all 3—chromosomal microarray analysis, fragile X testing, and karyotyping—as the first-line evaluation for both boys and girls with nonsyndromic ID of unknown etiology considering the yield of approximately 2% for fragile X testing and 4% for karyotyping for these cases. (24) Microarray analysis does not detect balanced translocations (which a karyotype is able to), point mutations, or low level of mosaicism. (25) If microarray
analysis reveals an abnormality, further genetic testing of the parents may be recommended. For females with severe to profound ID, testing for Rett syndrome (MECP2 gene) is recommended. (24)(25)

Consultation and collaboration with a clinical geneticist may be very useful in the evaluation of children with ID, especially those with unexplained ID, syndromic ID, or more severe levels of ID. Clinical geneticists and genetic counselors may also be helpful in the interpretation of the results of genetic testing. (25) A newer form of genetic testing, whole exome sequencing, may be able to identify a genetic cause in up to 40% of patients with unexplained ID; however, it is not widely available at this time, and the implications of using whole exome sequencing in the routine evaluation of all children with ID, wherein other genetic abnormalities not related to ID may be unearthed, is still not fully understood and must be explored further. (2)(25)

Inborn errors of metabolism account for a small percentage (approximately 5%-5%) of children with unexplained ID. (2)(7)(26) Testing for these conditions has been recommended for cases that are clinically suggestive of a metabolic disorder. Most of these conditions are associated with neurologic symptoms (ie, hypotonia, ataxia, dementia, epilepsy, spasticity), sensory deficits (visual and hearing impairment), and nonneurologic features, such as gastrointestinal symptoms, dermatologic findings, atypical odor, and problems in growth. Specific metabolic testing includes acylcarnitine profile, amino acids and urine organic acids, glycosaminoglycans, oligosaccharides, serum total homocysteine, purines, pyrimidines, and GAA/creating metabolites. (2) Recent reports have identified 89 inborn errors of metabolism associated with ID that are amenable to treatment. In line with this, a 2-tiered algorithm in testing for treatable forms of inborn errors of metabolism in a person with ID has been proposed. (26) Further studies are needed to fully comprehend the efficacy and implications of this approach in the evaluation of a child with unexplained ID. (7)(27)

Magnetic resonance imaging (MRI) may be helpful in the evaluation of children with nonsyndromic ID/GDD in the setting of abnormal neurologic findings such as microcephaly, macrocephaly, or focal neurologic signs, (28) with the likelihood of finding a structural abnormality increasing to 28% from a rate of 7.5% if the GDD/ID was isolated and not associated with abnormalities in head size or focal neurologic findings. The risk in the use of sedation or anesthesia in MRI studies, although low, should also be weighed in the evaluation of these children. An MRI is preferred over computed tomographic (CT) scan in identifying abnormal brain architecture and myelination and in the evaluation of deeper brain centers. A CT scan is useful to visualize calcifications, which may be present in prenatal infections such as toxoplasmosis and cytomegalovirus.

DIFFERENTIAL DIAGNOSES

In the evaluation of persons suspected of having ID, it is important to differentiate ID from neurodegenerative disorders, specific learning disorders, receptive/expressive language disorders, autism spectrum disorders, and sensory deficits (visual impairment and hearing impairment).

Neurodegenerative disorders present with significant regression in different aspects of functioning due to a progressive neurologic condition. This is in contrast to ID, whose etiology is nonprogressive (eg, genetic abnormality or a nonprogressive brain lesion). Specific learning disorders are neurodevelopmental disorders characterized by persistent difficulties in learning (eg, reading, mathematics, and/or written expression) that are not explained by and are not commensurate with one’s cognitive potential. Children with specific learning disorders can be differentiated from those with ID in that they may have impairment in specific areas of learning (eg, reading/phonological skills) but have age-appropriate adaptive skills and cognitive skills, whereas children with ID will have global impairment in cognitive and adaptive skills. Language deficits may also be present in ID, but in ID there are also significant nonverbal deficits, leading to a more global impairment in function. Autism spectrum disorder is frequently associated with ID but is a separate disorder characterized by persistent social-communication and social interaction deficits, restricted/repetitive patterns of behavior, and atypical sensory reactivities. (1) The cognitive level of children with autism may range from significant ID to normal intelligence. Last, in the evaluation of a child with suspected ID, it is important to rule out any significant visual and hearing impairment that may contribute to the child’s deficits in functioning.

MANAGEMENT

Special Education and Early Intervention

The mainstay of treatment and management of children with ID/GDD is the utilization of special education and early intervention programs. (6)(29) The Individuals with Disabilities Education Act provides individuals with ID/GDD the right to receive free and appropriate public education with goals and services as specified in their Individualized Education Program (IEP) or Individualized Family Service Plan (for children <3 years old). Studies have shown that early childhood education programs have long-term beneficial effects on cognition, language, academics (reading and
There has been research as well showing that participation of children with ID (e.g., Down syndrome) in early childhood educational programs may, at the very least, minimize the decline of intellectual functioning that occurs in these children. (32)(33)

During well-child visits, the pediatrician may detect developmental differences and delays through developmental surveillance or screening. Children who are suspected of having ID/GDD or other neurodevelopmental disorders should be referred to the state early intervention program (for children 0–3 years old) or to the Board of Education’s Committee on Preschool Special Education (for children 3–5 years old) or Committee on Special Education (for children 5–21 years old) for evaluation and services.

The Individuals with Disabilities Education Act stipulates that children with disabilities receive their educational services in the least restrictive environment that is possible and appropriate to address their educational needs. Because of this, there has been a thrust toward mainstreaming wherein children with disabilities, even those with ID, may participate in more typical school environments for most or part of the school day. An inclusion or collaborative team teaching classroom is such a setting where children with special needs participate in the same classroom as typically developing children under the tutelage of 1 main teacher and 1 or more special education teachers. Children with disabilities may also receive related services such as speech/language therapy, occupational therapy, physical therapy, and counseling. In addition, classroom modifications and accommodations may be given to children with learning or intellectual disabilities through Section 504 of the Rehabilitation Act, (6) a federal law that protects individuals with disabilities from discrimination in various settings, including the public school system. Enhancing a person with ID’s ability to communicate, not only through speech/language therapy but also through the use of a picture exchange communication system or augmentative communication devices, may be an important aspect of a child with ID’s educational plan. Compared with typically developing children, children with ID learn at a much slower pace and may require more frequent repetitions before mastering a skill. Furthermore, the gap between these 2 groups will be increasingly wider as the years go by—an important tenet when counseling parents.

For children with more severe impairment, such as those with moderate to profound ID, a self-contained classroom may be needed wherein there is a small student to teacher ratio and the provision of individual or group paraprofessionals as needed. The child’s IEP should reflect appropriate goals, which may be educational, vocational, or adaptive, while taking into consideration one’s strengths and weaknesses.

As the child reaches 16 years of age, the development of an Individualized Transition Plan would ensure continued support, beyond the educational realm, in areas such as employment, adult living skills, and recreation. (29)

Throughout this educational process, pediatricians play a key role, starting with the timely referral and identification of individuals with ID/GDD to being important advocates for their patients to receive services and interventions until they transition into adulthood. The Center for Parent Information and Resources (funded by the US Department of Education) offers helpful online information for pediatricians and parents about ID and the educational process, including the IEP and Individualized Transition Plan (http://www.parentcenterhub.org/intellectual/#school and http://www.parentcenterhub.org/transitionadult/).

Medical Home

The AAP and the US Department of Health and Human Services through its Healthy People 2010 have recommended that children, especially those with special health-care needs, which includes ID, receive “regular, ongoing, comprehensive care within a medical home.” (34) In the medical home model of care, the pediatrician in collaboration with other medical subspecialists and professionals such as social workers and community health workers work as a team in the care of children with special needs, who, in addition to their primary disability, may have significant comorbid medical and psychiatric conditions and family challenges. The involvement of the family and addressing its needs are important components of the medical home.

Management of Comorbid Medical Conditions. Individuals with ID, especially those with moderate to profound ID, may have comorbid medical conditions such as seizure disorders, cerebral palsy, gastrointestinal disorders, and respiratory problems, which may have a significant effect on their daily functioning, progress, and need for additional support. (i)(5) Other important medical issues to explore in the care of people with ID are matters of sexuality and abuse, obesity and nutrition, physical activity and fitness, dental issues, and pain management. In addition to referring to appropriate subspecialists, the pediatrician has a role in providing information and resources to families about the child’s disability, recommending healthy lifestyle options for diet and recreation, assuming the role of a conduit between the family and medical subspecialists, and being advocates for services that may address a patient’s and family’s needs. Online resources from the Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/ncbddd/actearly/pdf/parents_pdfs/intellectualdisability.pdf and https://www.cdc.gov/ncbddd/disabilityandhealth/healthyliving.html) and Parent Center
Management of Comorbid Mental Health Conditions. Thirty percent of individuals with ID may have comorbid mental health conditions. This rate is significantly higher than the rate observed in the general population. These mental health conditions include attention-deficit/hyperactivity disorder, depression, mood disorders, aggressive behaviors, and self-injurious behaviors. Behavioral interventions should be implemented in those with major behavioral difficulties, such as hyperactivity, aggressive behaviors, and self-injury. These interventions may be implemented in the home or school setting, with carryover to other settings to provide maximal benefit. Treatment with appropriate psychopharmacologic medications, based on target symptoms (eg, hyperactivity, aggressive behavior, self-injury), should be considered in those not fully controlled by behavioral measures, and referral to a child psychiatrist for medication management may be necessary.

Referral to State/Community Programs and Family Supports. It is important for the pediatrician to be aware of the state and community programs that are available for persons with ID and other developmental disabilities in their community. A social worker, who may be consulted within the practice (if available) or in community agencies, may be an invaluable resource in providing support for families and in directing them to the appropriate community programs. In New York State, children with significant ID and other developmental disabilities, such as autism, are directed to the New York State Office for People with Developmental Disabilities (https://opwdd.ny.gov/). After undergoing an eligibility evaluation, each child with a disability is assigned a service coordinator who assists the family in obtaining access to community programs, respite services, home care support and after-school programs, behavior-management training, transportation services, crisis intervention, etc. The pediatrician or social worker may also refer the child to entitlement programs such as Social Security and Medicaid, which may provide invaluable supports for families.

As a child with ID reaches adulthood, issues such as legal guardianship, transitioning to an adult health-care provider, and employment come to the forefront and must be addressed. There is growing research that shows that given appropriate support and guidance, persons with ID may strive for competitive or supportive employment. With these educational, medical, and community interventions, the ultimate goal is for persons with ID to reach their maximum potential as individuals and as members of the community.

Summary

- According to the definition, intellectual disability (ID) is a neurodevelopmental disorder that is characterized by deficits in both intellectual functioning and adaptive functioning (>2 SD below the mean as measured by standardized tests and questionnaires), with onset in the developmental period or younger than 18 years of age. The severity of ID is based on a person’s adaptive functioning and level of supports.
- Based on some research evidence as well as consensus, the initial approach to the evaluation for the etiology of the ID includes a thorough history, a detailed physical examination, and a focused evaluation based on the history and physical examination findings, which may include laboratory testing, genetic testing, and imaging.
- Based on some research evidence as well as consensus, the recommendation for the evaluation of nonsyndromic ID of unknown etiology includes genetic testing with chromosomal microarray analysis, fragile X testing, and karyotyping. For females with severe-profound ID, testing for Rett syndrome is also recommended.
- Based on some research evidence as well as consensus, the mainstay of treatment and management of ID/global developmental delay is the utilization of special education and early intervention programs through the Individuals with Disabilities Education Act. Individuals with ID, especially those with moderate to profound ID, should also be evaluated for comorbid medical and mental health conditions, which are more prevalent in this population than in the healthy population. Finally, children with ID, as with other children with special health-care needs, are best followed in a medical home-type setting where there is collaboration between the pediatrician, other health professionals, community workers, and the child’s family.

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/39/6/299.supplemental.

Intellectual Disabilities

Oscar Purugganan, MD, MPH
Columbia University Medical Center
New York, NY

References for this article are at http://pedsinreview.aappublications.org/content/39/6/299.
PIR Quiz

There are two ways to access the journal CME quizzes:
1. Individual CME quizzes are available via a handy blue CME link under the article title in the Table of Contents of any issue.
2. To access all CME articles, click "Journal CME" from Gateway's orange main menu or go directly to: http://www.aappublications.org/content/journal-cme.
3. To learn how to claim MOC points, go to: http://www.aappublications.org/content/moc-credit.

1. A 7-year-old girl was noted to have global developmental delay by the time she was in preschool. She has been otherwise healthy, with no medical concerns. She has delays in reading, writing, and math skills and is very immature compared with her peers. These findings were not obvious in preschool and kindergarten, although she did receive early intervention for speech delay. Her academic delays have become more noticeable in second grade. Which of the following best describes this patient’s intellectual functioning?
   A. Borderline intellectual functioning.
   B. Mild intellectual disability (ID).
   C. Moderate ID.
   D. Profound ID.
   E. Severe ID.

2. A 10-year-old boy with moderate ID and autism is brought to your office for evaluation. His maternal uncle and maternal grandfather have ID. He was noted to have an elongated face. His mother has early-onset menopause. His medical history is unremarkable for any head trauma or central nervous system infections, and he has no history of seizures. Which of the following is the most appropriate next step in diagnosis in this patient?
   A. Karyotyping.
   B. DNA testing for fragile X syndrome.
   C. Magnetic resonance imaging of his brain.
   D. MECP2 gene testing.
   E. Whole exome sequencing.

3. After performing a thorough history and physical examination of the patient in question 2, you start the diagnostic evaluation, the results of which are still pending. Which of the following is most likely to be seen on physical examination of this patient?
   A. Failure to thrive.
   B. Lish nodules on eye examination.
   C. Inguinal and axillary freckling.
   D. Macrocephaly.
   E. Skin ash leaf spot.

4. A 6-year-old girl has been diagnosed as having global developmental delay and macrocephaly. In the past year she has developed increased incoordination and ataxia as well as increasing academic challenges and marked difficulty learning new skills. The parents also report on and off gastrointestinal symptoms, including diarrhea, abdominal pain, and bloating. On physical examination she has no dysmorphic features and no abnormal physical findings. Which of the following is the most appropriate next step in diagnosis in this patient?
   A. Chromosomal microarray analysis.
   B. Fragile X testing.
   C. Karyotyping.
   D. Metabolic testing.
   E. Whole exome sequencing.

REQUIREMENTS: Learners can take Pediatrics in Review quizzes and claim credit online only at: http://pedsinreview.org.

To successfully complete 2018 Pediatrics in Review articles for AMA PRA Category 1 Credit™, learners must demonstrate a minimum performance level of 60% or higher on this assessment. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2020, however, credit will be recorded in the year in which the learner completes the quiz.

2018 Pediatrics in Review now is approved for a total of 30 Maintenance of Certification (MOC) Part 2 credits by the American Board of Pediatrics through the AAP MOC Portfolio Program. Complete the first 10 issues or a total of 30 quizzes of journal CME credits, achieve a 60% passing score on each, and start claiming MOC credits as early as October 2018. To learn how to claim MOC points, go to: http://www.aappublications.org/content/moc-credit.
5. A 3-year-old boy uses approximately 20 words functionally. He can follow simple single-step instructions. He is not yet toilet trained and does not seem to understand the concept of toileting. He has a very short attention span but no significant behavioral concerns. You interview the family and note that there are no family members who have been identified as having developmental delays. On physical examination, his head circumference is at the 99th percentile. The remainder of his physical examination findings are within normal limits. Which of the following is the most appropriate next step in evaluation in this patient?

A. Acylcarnitine profile.
B. An electroencephalogram.
C. Magnetic resonance imaging of his brain.
D. Serum amino acids and urine organic acids.
E. Whole exome sequencing.
### Intellectual Disabilities

Oscar Purugganan  
*Pediatrics in Review* 2018;39;299  
DOI: 10.1542/pir.2016-0116

| Updated Information & Services | including high resolution figures, can be found at:  
|-------------------------------|--------------------------------------------------|
| Supplementary Material        | Supplementary material can be found at:  
|                               | [http://pedsinreview.aappublications.org/content/39/6/299](http://pedsinreview.aappublications.org/content/39/6/299)  
| References                    | This article cites 28 articles, 11 of which you can access for free at:  
|                               | [http://pedsinreview.aappublications.org/content/39/6/299.full#ref-list](http://pedsinreview.aappublications.org/content/39/6/299.full#ref-list)  
| Subspecialty Collections      | This article, along with others on similar topics, appears in the following collection(s):  
|                               | **Medical Education**  
|                               | [http://classic.pedsinreview.aappublications.org/cgi/collection/medical_education_sub](http://classic.pedsinreview.aappublications.org/cgi/collection/medical_education_sub)  
|                               | **Journal CME**  
|                               | [http://classic.pedsinreview.aappublications.org/cgi/collection/journal_cme](http://classic.pedsinreview.aappublications.org/cgi/collection/journal_cme)  
|                               | **Community Pediatrics**  
|                               | [http://classic.pedsinreview.aappublications.org/cgi/collection/community_pediatrics_sub](http://classic.pedsinreview.aappublications.org/cgi/collection/community_pediatrics_sub)  
|                               | **Developmental/Behavioral Pediatrics**  
|                               | [http://classic.pedsinreview.aappublications.org/cgi/collection/developmental_issues_sub](http://classic.pedsinreview.aappublications.org/cgi/collection/developmental_issues_sub)  
|                               | **Cognition/Language/Learning Disorders**  
|                               | [http://classic.pedsinreview.aappublications.org/cgi/collection/cognition_language_learning_disorders_sub](http://classic.pedsinreview.aappublications.org/cgi/collection/cognition_language_learning_disorders_sub)  
|                               | **Children With Special Health Care Needs**  
|                               | [http://classic.pedsinreview.aappublications.org/cgi/collection/disabilities_sub](http://classic.pedsinreview.aappublications.org/cgi/collection/disabilities_sub)  
| Permissions & Licensing       | Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:  
|                               | [https://shop.aap.org/licensing-permissions/](https://shop.aap.org/licensing-permissions/)  
| Reprints                      | Information about ordering reprints can be found online:  
|                               | [http://classic.pedsinreview.aappublications.org/content/reprints](http://classic.pedsinreview.aappublications.org/content/reprints)  

Downloaded from [http://pedsinreview.aappublications.org/](http://pedsinreview.aappublications.org/) by 1471001 on March 29, 2020