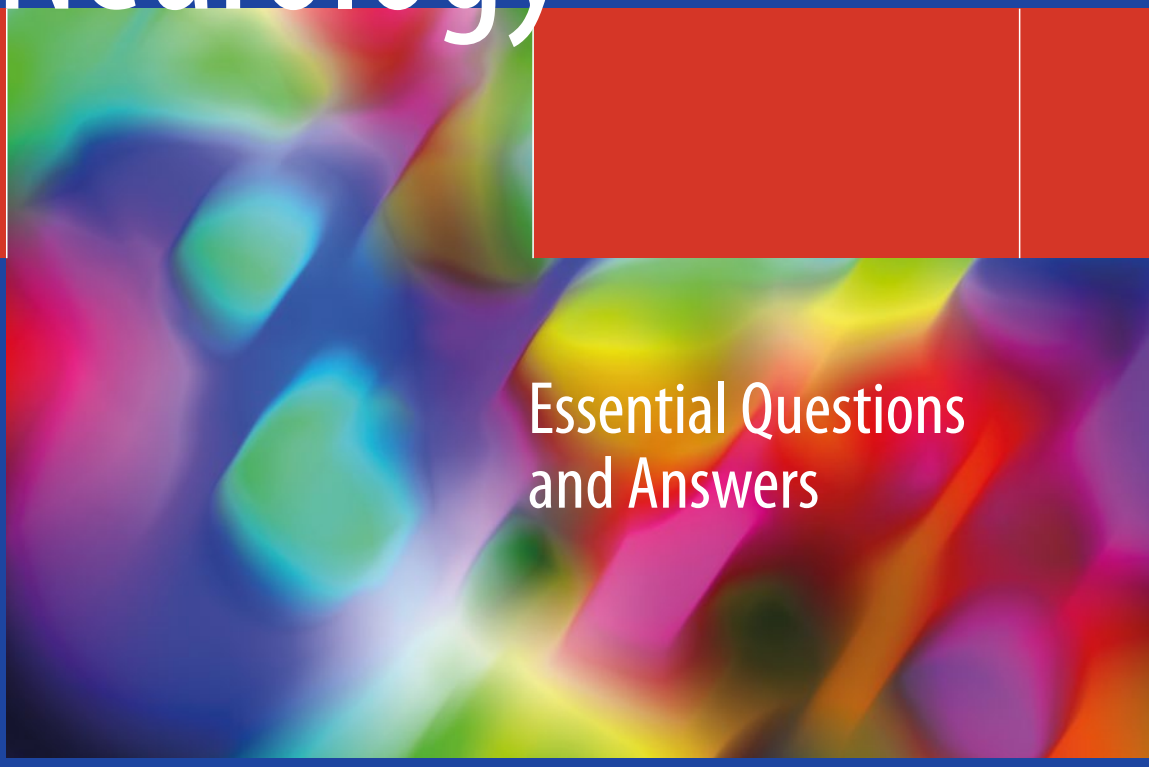
Yasser M. Awaad

Absolute Pediatric Neurology



Essential Questions and Answers

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I am dedicating this work to my beloved family, especially my father, Mahmoud Awaad, mother, Galila Jad and children, Rania, Ammar and Emmad Awaad.

A very special dedication to my wife, Ola Abdellatif, who blessed me with unwavering support throughout my life journey.

Yasser M. Awaad

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Autism

Y. M. Awaad, *Absolute Pediatric Neurology*, https://doi.org/10.1007/978-3-319-78801-2_1

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1. A 24 months old boy is referred for abnormal development and behavior. He has no use of speech to communicate his needs, has a limited repertoire of activities, and poor eye contact. He was diagnosed as autistic spectrum disorder by his primary care physician, but his parents are interested in finding out his specific diagnosis.
Which of the following tests can be used to best confirm his diagnosis and clarifying its type?
   A. Blood lead level and serum IgG for gluten sensitivity
   B. Chromosomal testing for 16p11.2 deletion/duplication
   C. Checklist for autism in toddlers (CHAT) or modified checklist (m-CHAT)
   D. Denver developmental screening test – revised (Denver II)
   E. PDD assessment scale/ screening questionnaire

Correct Answer is: C
Environmental factors might contribute in many children with autistic spectrum disorders, such as lead exposure or celiac disease, but testing for those factors do not diagnose ASD. It is not the first test to do, 16p11.2 deletion/duplication is associated with autism, and is not a test to diagnose autism. The m-CHAT is a screening testing of both parental information and examiner observations, and it is for 16–30 month toddlers. The Denver II is a screening device, and is no longer recommended when screening for autism. The PDD Assessment scale/ screening questionnaire is not designed as a health care professional test. It is given to parents/ caretakers for reaching the diagnosing of their children.

Suggested Reading

Article on PDD scale on ► Childbrain.com (► http://childbrain.com/pddq6.shtml).
Diagnostic and statistical manual of mental disorders, 4th ed. Washington DC: American Psychiatric Association; 1994.
Filipek PA, Accardo PJ, Ashwal G et al. International classification of diseases: diagnostic criteria for research, 10th ed. the World Health Organization. Practice parameter: screening and diagnosis of autism: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society. Neurology. 2000;55:468–479.

2. A 19 months old boy is referred for developmental delay evaluation. He was born at 37 weeks gestation as repeat cesarean section, birth weight of 3.0 kilograms. He rolled at 6 months, walked at 11 months, and said 3 words at 11 months. Currently he does not speaks any words, does not know body parts and will not follow one-step commands. Sleep habits are very poor, with frequent night awakenings. He has episodes of flapping movements of his hands and arms, last 20–30 min, but disappear if he was picked up, and reappear if he was put down. He will not point to objects and has variable eye contact.
Which of the following is the most likely diagnosis?
   A. Hearing loss
   B. Acquired auditory aphasia (Landau Kleffner syndrome)
   C. Mental retardation
   D. Autistic disorder
   E. Childhood schizophrenia

Correct Answer is: D
Diagnosis of autistic spectrum disorders before the age of 2 years can be challenging, and other conditions should to be considered. Hearing loss is very important to rule out with formal hearing testing. This patient has a number of features that assist with making the diagnosis of autistic disorder, including restricted language and social skills and motor stereotypies.

Suggested Reading

- Zwaigenbaum L, Bryson S, Lord C, Rogers S, Carter A, Carver L, Chawarska K, Constantino J, Dawson G, Dobkins K, Fein D, Iverson J, Klin A, Landa R, Messinger D, Ozonoff S, Sigman M, Stone W, Tager-Flusberg H, Yirmiya N. Clinical assessment and management of toddlers with suspected autism spectrum disorder: insights from studies of high-risk infants. Pediatrics. 2009;123(5):1383–91.
- Wong V, Hui LH, Lee WC, Leung LS, Ho PK, Lau WL, Fung CW, Chung BA. Modified screening tool for autism (Checklist for Autism in Toddlers [CHAT-23]) for Chinese children. Pediatrics. 2004;114(2):e166–76.

3. An 8-year-old boy with "behavioral problems" and an intense preoccupation with trains that started at 3 years of age. There were no perinatal complications and normal early developmental milestones. He has no close friends, and difficulties in social settings at school. He has no problem in speech and language development, but he is unusually verbose, tangential or circumstantial, and at times exhibits inappropriate humor. He is extremely sensitive to stimulation, and has had difficulty falling asleep with intermittent awakenings during the night. He was inattentive during the evaluation, but his neurological examination was normal.
   Which of the following is the most likely diagnosis?
   A. Autism
   B. Conduct disorder
   C. Asperger's syndrome
   D. Attention deficit hyperactivity disorder
   E. Depression

Correct Answer is: C
Asperger syndrome is an autistic spectrum disorder characterized by poor social interaction and the presence of restricted, stereotyped patterns of behavior and interests. Asperger syndrome patients often exhibit stereotyped behaviors and an intense preoccupation with a narrow activity or interest which is not required for diagnosis. In general, there is no delay in cognitive or language development, self-help or adaptive skills, or interest in the environment. Differential diagnosis includes autism, pervasive developmental disorder (not otherwise specified), attention deficit hyperactivity disorder, obsessive compulsive disorder, selective mutism, childhood disintegrative disorder.

Suggested Reading

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders DSM-IV-TR. 4th ed. Washington DC: American Psychiatric Association; 2000.
- Khouzam HR, El-Gabalawi F, Pirwani N, Priest F. Asperger's disorder: a review of its diagnosis and treatment. Compr Psychiatry. 2004;45(3):184–91.
- McPartland J, Klin A. Asperger's syndrome. Adolesc Med Clin. 2006;17(3):771–88.

4. The choices are genetic or environmental risk factors for developing autism spectrum disorders and/or intellectual disabilities **EXCEPT**:
   A. More than 200 CGG trinucleotide repeats
   B. De novo mutations in the SCN2A (sodium channel, voltage-gated, type II, alpha), STXBP1 (syntaxin binding protein 1), SCN1A (sodium channel, voltage-gated, type I, alpha), or SYNE1 (synaptic nuclear envelope protein 1) genes
   C. TSC-1 (Tuberous Sclerosis Complex) gene mutations
   D. Deletions within the MECP2 gene
   E. Older parental age

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Correct Answer is: E
Older paternal age at the time of birth has been considered as a risk factor for developing autism spectrum disorders (ASD), no sufficient evidence to validate this concern. Greater than 200 CGG trinucleotide repeats is diagnostic of Fragile X syndrome, it might have ASD manifestations and/or intellectual disability. TSC-1 mutations can cause Tuberous Sclerosis, which often has concomitant diagnoses of ASD and epilepsy. Deletions within the MECP2 gene are confirmatory of Rett Syndrome, which can manifest with ASD, intellectual disability, and epilepsy.

Suggested Reading

- Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: comprehensive meta-analysis. Pediatrics. 2011;128:344–55.
- Iossifov I, Ronemus M, Levy D, et al. De novo gene disruptions in children on the autistic spectrum. Neuron. 2012;74:285–99.
- Sebat J, Lakshmi B, Malhotra D, et al. Strong association of de novo copy number mutations with autism. Science. 2007;316:445–9.

5. Which statement about autism spectrum disorders and epilepsy is true?
   A. The incidence of epilepsy autism spectrum disorders is similar for those with mild, moderate or severe manifestations
   B. The incidence and prevalence of epilepsy in autism spectrum disorders is independent of concomitant, co-morbid neurological disorders/diagnoses
   C. The biological and molecular mechanisms causing or leading to epilepsies or autism spectrum disorders are not similar and dependent
   D. EEG in autism spectrum disorders is not a useful test because of behavioral non-compliance
   E. The risk of epilepsy in children and adolescents with autism spectrum disorders ranges from 6–26%, and it is higher in patients with cerebral palsy or intellectual disabilities

Correct Answer is: E
The incidence of epilepsy in children and adolescents with autism spectrum disorders is higher in children with intellectual disabilities and cerebral palsy. Mortality rates increase in patients having autism associated with epilepsy. The growing evidence that epilepsies and ASD shares common biological etiologies and mechanisms, increase interest and research in devising interventions that can change the course of both diseases.

It is difficult to detect seizures in patients with autism spectrum disorders, and acquiring electroencephalograms can be challenging in individuals with behavioral challenges. With such individuals, utilization of behavioral interventions can be helpful, and technologies utilizing electrodes not requiring scalp abrasion, glues or pastes, allow for successful EEG acquisition, which can yield important information about clinical and subclinical epilepsies.

Suggested Reading

- Amiet C, Gourfinkel-AnI, Bouzamondo A, et al. Epilepsy in autism is associated with intellectual disability and gender: evidence from a meta-analysis. Biol Psychiatry. 2008;64:577–82.
- Bolton PF, Carcani-Rathwell I, Hutton J, et al. Epilepsy in autism: features and correlates. Br J Psychiatry. 2011;198:289–94.
- McVicar KA, Ballaban-Gil K, Rapin I. et al. Epileptiform EEG abnormalities in children with language regression. Neurology. 2005;65:129–31.
- Pickett J. et al. Mortality in individuals with autism, with and without epilepsy. J Child Neurol. 2011;26:932–9.

6. A 4 year old boy is here for a neurological evaluation. You noted that he does not have joint attention, makes minimal eye contact, has echolalia and repetitively spins instead of playing with the toys in the room. You consider the diagnosis of Autism Spectrum Disorder. In taking the history, the mother states that she had taken valproic acid and topiramate for severe migraines during the pregnancy. The valproic acid was added after the first trimester. She had also taken folic acid. She asked you if any of the medications could have contributed to the child's condition.

Your response would be:

A. Taking Valproic acid only increases the risk of spinal tube defects
B. Only thalidomide has been shown to increase the risk of Autism
C. Taking topiramate does not cause any birth defects
D. The risk of autism increased 3-fold for children born to mothers who took VPA during pregnancy
E. The risk of autism is similar to spina bifida; it only increases during first trimester exposure

Correct Answer is: D

Thalidomide and Valproic Acid have been shown to increase the risk of Autism in utero exposures. Valproic Acid exposure can increase the risk of neural tube defects is a well-known fact. The study by Christensen et al. and the commentary by Cynthia Harden revealed there "were an association of in utero VPA exposure and the risk of autism determined from a population-based study utilizing Danish national medical databases. Children born between 1996 and 2006 were followed for the documented occurrence of autism up to 14 years of age, with a mean follow-up of 9 years. Children born to mothers who took VPA during pregnancy, autism risk increased 3-fold and the risk of autism spectrum disorder (ASD) increased 5-fold over the general population risk. The absolute risk to VPA-exposed children was less than 5%, although the upper 95% confidence interval (CI) limit for ASD was 7.49%. There was no contribution of maternal epilepsy to the risk of VPA use. Hypospadias and spina bifida and occurs with first trimester exposure, but the autism risk was present in this study with VPA exposure starting at any trimester during pregnancy."

In Thalidomide exposure, there was a 50 fold higher rate of Autism in those with thalidomide embryopathy than in the general population.

The risk of oral clefts in infants exposed to topiramate during the first trimester of pregnancy has been increases according the data from the North American Antiepileptic Drug (AED) Pregnancy Registry. Infants exposed to topiramate as a single therapy experienced a 1.4% prevalence of oral clefts, compared with a prevalence of 0.38–0.55% in infants exposed to other antiepileptic drugs.

Suggested Reading

- Harden, C. In utero valproate exposure and autism: long suspected, finally proven. Epilepsy Curr. 2013;13(6):282–4.
- Christensen J, Grønborg TK, Sørensen MJ, Schendel D, Parner ET, Pedersen LH, Vestergaard M. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA. 2013;309(16):1696–703.
- Strömland K, Nordin V, Miller M, Akerström B, Gillberg C. Autism in thalidomideembryopathy: a population study. Dev Med Child Neurol. 1994;36(4):351–6.
- Risk of oral birth defects in children born to mothers taking topiramate. FDA NEWS RELEASE, March 4, 2011.

1

7. An 11-year-old boy came for a neurologic evaluation because of "odd behavior". He and his family recently relocated from another state. He does not maintain good eye contact when you tried to engage him. His parents mentioned that he had no friends and is not very affectionate with family. He is methodical and rigid in his patterns, getting upset if there is a change in his routine. Also they mentioned that he is fixated on following the statistics of his favorite football team. He does very well in school. There is no history of language or cognitive impairment.
Which of the following is the most correct diagnosis?
   A. attention deficit hyperactivity disorder
   B. autism spectrum disorder
   C. Landau-Kleffner syndrome
   D. Rett disorder
   E. Tourette syndrome

Correct Answer: B
This patient has the main symptoms of autism spectrum disorder, including lack of social interaction, as well as restrictive and repetitive behaviors. The new DSM V eliminates the diagnosis of Asperger syndrome (which fits this patient best because of intact language function, which is characteristically impaired in DSM IV autism symptom complex) in favor of including these patients in the broader category of "autism spectrum disorder". This patient's presentation is not suggestive of ADHD. Rett syndrome is associated with regression of language abilities and hand stereotypies, typically seen in girls (X-linked dominant). Tourette syndrome is a tic disorder, commonly with comorbid ADHD and OCD.

Suggested Reading

- Pellegrino L, Liptak GS. Consultation with the specialist: asperger syndrome. Pediatr Rev. 2011;32(11):481–9.
- Sugden SG, Corbett BA. Autism-presentation, diagnosis and management. Continuum Lifelong Learning Neurol. 2006;12(5):47–59.

8. A 4-year-old boy presents with a speech delay. He was a full term, with no prenatal or perinatal complications. He began walking at 13 months of age, is able to feed himself with utensils. He says many different words during the day; however most of this speech is repetition of things he hears on the television or from his family. He has no interactive play and does not identify body parts. He has no chronic medical illnesses and takes no medication. No family history of developmental delays. There have been no difficulties with feeding or swallowing. He does not have eye contact and does not go to his parents for reassurance. He makes several grunting sounds; a brief echolalic speech is produced. When given blocks to stack, He arranges blocks in a straight line. The rest of his neurological exam is normal for age. Hearing testing was normal one month ago.
Which of the following diagnoses is most likely for the child's language delay?
   A. autism spectrum disorder
   B. cerebral palsy
   C. congenital perisylvian syndrome
   D. Landau-Kleffner syndrome
   E. Menkes disease

Correct Answer is: A
Delays in acquisition of language are common in the pediatric population. Although isolated expressive or mixed expressive and receptive language delays are two prominent developmental disabilities of childhood, often there are clues from the history or physical exam that suggest

another possible diagnosis. You cannot rely on hearing test to be performed to exclude congenital or acquired hearing loss, even if the newborn hearing screen was normal. If, in addition to the language delay, there is an impairment of social interaction (in this case suggested by poor eye contact, lack of sharing attention with caregiver (interactive play), an autism spectrum disorder is likely. Milder subtypes of the spectrum include pervasive developmental disorder (PDD) and Asperger syndrome. Patients with PDD may have normal nonverbal intelligence, and may have some segments of cognitive ability that are quite advanced. Patients with Asperger syndrome may have typically developed language skills, but are quite impaired in the social arena. There are multiple etiologies that may lead to an autistic phenotype, though in most cases a formal etiology is not discovered. When there is an associated severe intellectual disability present, testing to include chromosome microarray, fragile X evaluation and MRI of the brain may be considered. The incidence of autism clearly is increasing with time, likely due to genetic factors, though other environmental factors have additionally been proposed. Large meta-analytic studies have not shown vaccination to be a causative factor. Early identification of the child with autism is important, as the only clearly beneficial treatment is early institution of autism specific therapy such as applied behavioral analysis (ABA therapy). Even with early therapy, failure to develop language before the age of 5 is an extremely poor prognostic sign. Cerebral palsy is defined specifically by static delays in motor control due to an early insult or malformation of the brain. Though often associated with language and cognitive delay, this diagnosis strictly pertains to a motor disturbance (most commonly muscle spasticity). Congenital bilateral perisylvian syndrome is a rare, usually sporadic, disturbance in neuronal migration that results in a bilateral thickened cortex (pachygyria) in the sylvian and Rolandic regions. All affected children have not only a delay in language (presumably from the disorganized cortex in the Broca region) but also a prominent pseudobulbar palsy causing prominent dysphagia and feeding difficulties. Epileptic encephalopathies such as Landau-Kleffner syndrome (LKS) are quite rare, especially in comparison to the 1:150 incidence of primary autism disorders, though should be considered in a child who develops typical language and social skills prior to age 2, and then undergoes a period of regression between 2–4 years of age, often associated with development of clinical seizures. Occasionally the regression will ensue prior to the appearance of the ictal events. Electroencephalography in LKS demonstrates electrical status epilepticus of sleep (ESES). Treatment may be resistant to traditional anticonvulsants (such as valproic acid or levetiracetam) and may require high dose benzodiazepines nightly and/or corticosteroid treatment. Response of the electrical features of the syndrome usually leads to improvement in the encephalopathy, but early recognition and aggressive management are essential. Menke's syndrome is a disorder of copper metabolism and is apparent at birth with severe hypotonia and sparse, brittle hair and early onset of epilepsy. Seizures are also a commonly associated problem. Although it is important to expand the diagnostic evaluation of the child with autistic-like behavior associated with significant loss of previously acquired skills (regression), many of these patients will not have a specific etiology discovered and will be diagnosed simply with a regressive form of autism. Up to one-third of children with autism experience a regression in skills (typically restricted to language and social skills and sparing motor function) between the ages of 1 and 3 for reasons as of yet unknown.

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Suggested Reading

Fenichel GM. Clinical pediatric neurology: a signs and symptoms approach. 6th ed. Philadelphia: Saunders Elsevier; 2005. p.119–21.

9. A 4-year-old boy was seen by his primary care physician. The family mentioned that he is "emotionless" as compared with his affectionate siblings. He never had eye contact. He does not like to be hugged or kissed and does not play with others. He prefers to sit alone in his room, playing with the racing cars, although he has several other toys. He often flaps his arms at his sides and sometimes when upset will repeatedly bang his forehead on the nearest piece of furniture or on a wall. He has few words in his vocabulary, but not as many as his siblings did at his age.
What is your most likely diagnosis?
   A. Autism
   B. Avoidant personality disorder
   C. Depression
   D. Schizophrenia
   E. Schizoid personality disorder

Correct Answer: A

The most likely diagnosis is autism. Autistic spectrum disorder is characterized by the triad of impaired social skills, impaired communication skills, and restricted repertoire of activities and interests. Impaired communication skills include both verbal and nonverbal skills. Social skill abnormalities include lack of eye contact or atypical eye contact, failure to develop peer relationships, and lack of emotional reciprocity. Motor stereotypies, repetitive voluntary behaviors such as those described here, lack of flexibility, preoccupation with specific objects or part of an object, and ritualistic patterns of behavior occur. This spectrum is broad, ranging from high-functioning individuals as seen in Asperger disorder to nonverbal children with little interaction and sometimes no language skills. Cognitive delay is not a part of the diagnostic criterion but may be an associated feature, although supernormal IQs may occur in some. Some improvements occur in adolescence, although seizures, mood disorders, or other comorbidities may also emerge. A genetic basis has been considered based on the high concordance rates among monozygotic twins and increased incidence in families with another child with autism. Neuropathology seen in patients with autism include under-development of limbic structures and reduced cerebellar Purkinje cells. Other genetic and metabolic disorders have been associated with autism, including neurofibromatosis, Down syndrome, fetal alcohol syndrome, and peroxisomal disorders. A diagnostic workup might be indicated for these disorders. Personality disorder cannot be made at this time, although some of the personality disorders include rigid behavior.

This patient does not meet diagnostic criteria for depression and schizophrenia.

Suggested Reading

Comprehensive review in clinical neurology: a multiple choice question book for the wards and boards ©2011 Wolters Kluwer Health Lippincott Williams & Wilkins. All rights reserved.

10. A 20-month-old boy has been evaluated for evaluation severe expressive and receptive language delay. He cannot point and pulls his parents around the house to indicate his needs. He has eye contact occasionally. He lines up his toys and gets upset when they are taken out of order. He flaps his hands when he is excited. On physical exam, he has two hypo-pigmented macules on his back.
What is your next step in his evaluation?
   A. Fragile X testing
   B. High resolution chromosomes
   C. EEG
   D. Modified Checklist for Autism in Toddlers
   E. Skull X-Rays

Correct Answer is: D
The child clinical presentation is classical for autism. Autism is a neurodevelopmental disorder characterized by impaired social communication, delayed expressive and receptive language and stereotypic behavior. The language disorder is a delay in the development of spoken language or difficulties sustaining speech. This is also a social disorder with marked difficulty in the use of nonverbal behaviors like gestures. There are restricted patterns of behavior like hand flapping, twisting or complex body movements. There may be absence of imaginative play. The cause for most cases of autism is unknown. Genetic disorders may be associated with autism spectrum disorders, Rett's syndrome, Fragile X and tuberous sclerosis complex. Early identification of Autism will allow specific interventions to improve the outcome. The Modified checklist for autism in toddlers is an easy tool to use for the pediatrician or primary provider. It is highly recommended that a multidisciplinary team that specializes in children with these disorders do the evaluation. The most common measures used include the Childhood Autism rating scales (trained observer), Gilliam Autism rating scale (parents report). The gold standard is the Autism Diagnostic Observation Schedule (ADDOS) or the Autism Diagnostic Interview-Revised (AIDR). The hypo-pigmented spots raise concern of tuberous sclerosis, so an MRI might be indicated.

Suggested Reading

De los Reyes EC, Roach ES. In: Cecil's essential of medicine. Andreoli T. Benjamin I, Griggs R, Wing E, editors. Philadelphia: Saunder Elsevier; 2010 p. 1192–22.

11. The mother of a 5–year-old autistic boy is planning to have another child. She is asking you if there is a possibility that her next child will be affected with the same disorder. **What testing would you do to help counsel the family?**
    A. Chromosomal microarray analysis
    B. Mitochondrial point mutation testing
    C. Head MRI
    D. EEG
    E. Serum amino acids

Correct Answer is: A
Genetic studies in families indicate a 5% recurrence rate. Although the cause of autism is not clear, most studies showed that the cause is most likely genetic. Comparative genomic hybridization (microarray or oligo array) offers high resolution genome wide screening of segmental genomic copy number variations. Microdeletions and duplications can be detected by this technique. De novo deletions and duplications offer insights to this well-recognized disorder. Due to its increasing widespread availability it has offered insight to the etiology of autism and autistic spectrum disorders. The most common abnormalities include maternally inherited duplication of Chromosome 15, de novo or inherited duplications of 16p 11.2.

Suggested Reading

Shen Y, Dries KA, Holm IA et al. Clinical genetic testing for patients with autistic spectrum disorders. Pediatrics. 2010. 125:e727–35.

12. A 12-year-old boy with normal early developmental milestones comes to you for behavioral difficulties. He has long history of difficulties interacting with peers. He prefers adults and younger children. Lately, he became aggressive towards his classmates and even hit another child who was making fun of him. He has excellent grades in math but is failing in classes like English and reading. His favorite is Robotics. He has normal exam except monotonous, dysprosodic speech.

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What is your diagnosis?

A. Asperger's syndrome
B. Sensory processing disorder
C. Pervasive developmental disorder
D. Mental retardation
E. Verbal apraxia

Correct Answer is: A

Asperger's syndrome is a neurodevelopmental disorder characterized by deficits in social interactions, pragmatic language and restricted interests. Usually children with the syndrome have normal acquisition of early developmental language skills with average cognitive skills. Diagnosis is usually around 6 years of age since the increasing social demands of school may lead to evaluation of the atypical behaviors. Language is characterized as "pedantic". Although verbal in specific topics of their interest, Asperger patients may have difficulty expressing their feelings or relating to others, especially with their peers.

Suggested Reading

- Levy SE, Hyma SL, Pinto-Martin J. Autism spectrum disorders. In: Accardo PJ, ed. Neurodevelopmental disabilities in infancy and childhood. Vol. 2, 3rd. Baltimore: Brooke's Publishing; 2008. p. 497.
- Place-Johnson C, Myers SM, Council on children with disabilities. identification and evaluation of children with autism spectrum disorders. Pediatrics. 2007. p. 1182–1215.

13. The family of a 6-year-old boy diagnosed with autism would like to know what the best treatment interventions are for their son. Physical exam is normal.

What is your advice to the family?

A. Behavioral intervention with Applied Behavioral Analysis
B. Hyperbaric oxygen treatments
C. Gluten and casein free diet
D. Chelation therapy
E. Vitamin and mineral supplements

Correct Answer is: A

Early diagnosis is recommended in children with autistic spectrum disorders. The management of autism is based on the principles of behavioral and educational intervention. Applied Behavioral Analysis is the process of applying interventions that are based on the principles of learning, derived from experimental psychology research, to systematically change behavior and to demonstrate that the interventions used are responsible for the observable improvement in behavior. ABA methods are used to increase and maintain desirable adaptive behaviors, reduce interfering maladaptive behaviors (or narrow the conditions under which they occur), teach new skills, and generalize behaviors to new environments or situations. Alternating program that is well accepted is structured teaching or the TEACCH program. The bases of the program, emphasize structure and organization. Other interventions include speech/language therapy and occupational therapy. However, these are not case controlled studies showed improvements on gluten and casein free diet. Media and certain parent groups have advocated the management of autism with multiple vitamins and supplements, however, there are no case controlled studies to determine efficacy.

Suggested Reading

- Myers S, Place-Johnson C, Council on children with disabilities. Management of children with autism spectrum disorders. Pediatrics. 2007. p. 1162–82.
- Filipek PA, Accardo PJ, Ashwal G et al. Practice parameter: screening and diagnosis of autism: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society. Neurology. 2000;55:468–79.

14. You evaluate A 9 years-old boy with a longstanding diagnosis of autism spectrum disorder-moderate/severe. His family describes occasional

"freeze episodes", characterized by a general cessation of movement in a fixed posture, during which time he is awake, alert but is not interactive or conversant. He has a history of seizures, happens approximately once a year while maintained on lamotrigine.

All the mentioned below differential diagnostic entities warrant consideration, which is most consistent with the boy's history:

A. GLUT-1 deficiency
B. Dravet's syndrome
C. Landau-Kleffner syndrome
D. Disorder of Cerebral Folate Metabolism
E. Fragile X syndrome

Correct Answer is: D

The history is consistent with recurrent episodes of catatonia-like episodes. Catatonia in individuals with autism spectrum disorders has been reported to be associated with Disorders of Cerebral Folate Metabolism, and in some cases can be improved with the administration of folinic acid. GLUT-1 deficiency can be associated with epilepsy and autism spectrum disorders, but usually intractable epilepsies relatively uncontrolled by antiepileptic drugs, but responsive to the ketogenic diet. Dravet's Syndrome is associated with genetic mutations of the SCN1A gene, and lamotrigine might worsen the seizures. Landau-Kleffner Syndrome is associated with language regression and autism spectrum disorders, with epileptiform activity seeing during sleep, and classically without observable seizure events. Fragile X syndrome is associated with intellectual disability, and can have associated with epilepsy or autism spectrum disorders. Other than Disorders of Cerebral Folate Metabolism, the other entities listed are not generally associated with catatonia.

Suggested Reading

- Ho A, Michelson D, Aaen G, Ashwal S. Cerebral folate deficiency presenting as adolescent catatonic schizophrenia: a case report. J Child Neurol. 2010;25:898–900.
- Hyland K, Shoffner J, Heales SJ. Cerebral folate deficiency. J Inherit Metab Dis. 2010;33:563–70.

15. A 5-month-old baby has refractory infantile spasms. A cardiac rhabdomyoma was diagnosed prenatally. Her skin has multiple hypomelanotic macules. Her Head MRI shows frontal cortical tubers. The EEG reveals multifocal temporal regions discharges.

What symptom in her history puts her at risk for developing autism?

A. Temporal lobe focus
B. Hypomelanotic macules
C. Cardiac rhabdomyoma
D. Age of developing infantile spasms
E. Frontal cortical tubers

Correct Answer is: A

Current evidence indicates that the likelihood of a child with tuberous sclerosis developing an autism spectrum disorder is greater if the child has a mutation in the TSC2 gene, although autism can and does develop in children with TSC1 mutations. The likelihood is also greater if the child has early-onset infantile spasms that are difficult to control, especially if there is an epileptiform focus in the temporal lobes. The emerging evidence is consistent with the notion that early onset electrophysiological disturbances within the temporal lobes has a deleterious effect on the development and establishment of key social cognitive representations concerned with processing social information, especially from faces.

Suggested Reading

- Bolton, PF. Neuroepileptic correlates of autistic symptomatology in tuberous sclerosis. Ment Retard Dev Disabil Res Rev. 2004;10(2):126–31.

16. A 6-year-old boy is referred by his school teacher because he is having difficulty with his peers. His mom reported that he does not interact with others. He only likes to talk about and play with the video game Minecraft. He does not understand peer teasing. He does not understand emotional cues. His mom states that he has a great vocabulary and is doing well academically. On examine, he has no eye contact, has limited facial expression and does not have joint attention. He cannot engage in a back and forth conversation but tells you about Minecraft. You consider whether he fulfills the criteria for an Autism Spectrum Disorder.

Which below choice is not included in the DSM V Criteria for Autism Spectrum Disorder?

A. Deficits in social-emotional reciprocity
B. Deficits in nonverbal communicative behaviors used for social interaction
C. Deficits in developing and maintaining relationships, appropriate to developmental level
D. Stereotyped repetitive movement, speech, or use of objects
E. Delays in language

Correct Answer is: E

The DSM V that was published in 2013 revealed changes in the criteria for ASD. The criteria no longer include language delays.

Diagnostic Criteria include:

1. **Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive, see text):**
   1. **Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.**
   2. **Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.**
   3. **Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.**

Specify current severity:

Severity is based on social communication impairments and restricted repetitive patterns of behavior.

2. **Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):**
   1. **Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).**
   2. **Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day).**

3. **Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).**
4. **Hyper- or hypo reactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).**

Specify current severity:

Severity is based on social communication impairments and restricted, repetitive patterns of behavior.

3. **Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).**
4. **Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.**
5. **These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.**

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Specify if:

- **With or without accompanying intellectual impairment.**
- **With or without accompanying language impairment.**
- **Associated with a known medical or genetic condition or environmental factor.**
- **Associated with another neurodevelopmental, mental, or behavioral disorder.**
- **With Catatonia.**

Suggested Reading

- Diagnostic and statistical manual of mental disorders: DSM-5

17. A 4-month-old baby girl has refractory infantile spasms. Prenatally she was found to have a cardiac rhabdomyoma. She has multiple hypomelanotic macules on her skin. Brain MRI reveals frontal cortical tubers. The EEG reveals multifocal discharges; predominantly in the frontal regions.
What factor puts her at risk for developing autism?
    A. Having refractory infantile spasms
    B. Having hypomelanotic macules
    C. Having a cardiac rhabdomyoma
    D. Having frontal cortical tubers
    E. Having bifrontal discharges

Correct Answer is: A

Recent studies showed that the likelihood of a child with tuberous sclerosis developing an autism spectrum disorder is greater if the child has a mutation in the TSC2 gene, although autism can and does develop in children with TSC1 mutations. The likelihood will increase if the child has early-onset infantile spasms that are difficult to control, especially if there is an epileptiform focus in the temporal lobes. The emerging evidence is consistent with the notion that early onset electrophysiological

disturbances within the temporal lobes has a deleterious effect on the development and establishment of key social cognitive representations concerned with processing social information, perhaps especially from faces.

Suggested Reading

Bolton, PF. Neuroepileptic correlates of autistic symptomatology in tuberous sclerosis. Ment Retard Dev Disabil Res Rev. 2004;10(2):126–31.

18. A 4-year-old boy with speech delay came to your office for an evaluation. He was born at full term, with no prenatal or perinatal complications. He walked at 14 months of age, is able to feed himself with utensils. He uses several words during the day; most of them is repetition of things he hears on the television or from his family. He has no interactive play and does not identify body parts. He has no history of chronic medical illnesses and takes no medication. He has no family history for any developmental delays. There have been no difficulties with feeding or swallowing. During his examination he does not make sustained eye contact and does not go to his parents for reassurance. He makes several grunting sounds; a brief echolalic speech is produced. When given blocks to stack, he puts them in a straight line. His neurological exam is normal for age. His hearing is normal and confirmed by an audiology examination one month ago.
What is most likely diagnose for the boy's language delay?
A. autism spectrum disorder
B. Landau-Kleffner syndrome
C. cerebral palsy
D. congenital perisylvian syndrome
E. Menke's disease

Correct Answer is: A
Language acquisition delays in the pediatric age group population is common. Although isolated expressive or mixed expressive and receptive language delays are two common developmental disabilities of childhood, usually there are clues from the history or physical exam that suggest another possible diagnosis. It is important for a hearing test to be performed to exclude congenital or acquired hearing loss, even if the newborn hearing screen was normal. If, in addition to the language delay, there is an impairment of social interaction (in this case suggested by poor eye contact, lack of sharing attention with caregiver (interactive play), an autism spectrum disorder is likely. Milder subtypes of the spectrum include pervasive developmental disorder (PDD) and Asperger syndrome. Patients with PDD may have normal nonverbal intelligence, and may have some segments of cognitive ability that are quite advanced. Patients with Asperger syndrome may have typically developed language skills, but are quite impaired in the social arena. There are multiple etiologies that may lead to an autistic phenotype, though in most cases a formal etiology is not discovered. When there is an associated severe intellectual disability present, testing to include chromosome microarray, fragile X evaluation and brain MRI may be considered. The incidence of autism is on the raise, likely due to genetic factors, though other environmental factors have additionally been proposed. Vaccination is not a causative factor based on a large meta-analytic studies. Early autism diagnosis is important, as the only clearly beneficial treatment is early institution of autism specific therapy such as applied behavioral analysis (ABA therapy). Even with early treatment, failure to develop language before the age of 5 is an extremely poor prognostic

sign. Epileptic encephalopathies such as Landau-Kleffner syndrome (LKS) are quite rare, especially in comparison to the 1:150 incidence of primary autism disorders, though should be considered in a child who develops typical language and social skills prior to age 2, and then undergoes a period of regression between 2–4 years of age, often associated with development of clinical seizures. Occasionally the regression will occur before the appearance of the ictal events. EEG in LKS demonstrates electrical status epilepticus of sleep (ESES). Treatment may be resistant to traditional anticonvulsants (such as valproic acid or levetiracetam) and may require high dose benzodiazepines nightly and/or corticosteroid treatment. Response of the electrical features of the syndrome usually leads to improvement in the encephalopathy, but early recognition and aggressive management are essential. Cerebral palsy is defined specifically by static delays in motor control due to an early insult or malformation of the brain. Though often associated with language and cognitive delay, this diagnosis strictly pertains to a motor disturbance (most commonly muscle spasticity). Congenital bilateral perisylvian syndrome is a rare, usually sporadic, disturbance in neuronal migration that results in a bilateral thickened cortex (pachygyria) in the sylvian and Rolandic regions. All affected children have not only a delay in language (presumably from the disorganized cortex in the Broca region) but also a prominent pseudobulbar palsy causing prominent dysphagia and feeding difficulties. Seizures are also a commonly associated problem. Menke's syndrome is a disorder of copper metabolism and is apparent at birth with severe hypotonia and sparse, brittle hair and early onset of epilepsy. Although it is important to expand the diagnostic evaluation of the child with autistic-like behavior associated with significant loss of previously acquired skills (regression), many of these patients will not have a specific etiology discovered and will be diagnosed simply with a regressive form of autism. Up to 1/3 of children with autism experience a regression in skills (typically restricted to language and social skills and sparing motor function) between the ages of 1 and 3 for reasons as of yet unknown.

Suggested Reading

Fenichel GM. Clinical pediatric neurology: a signs and symptoms approach. 6th ed. Philadelphia: Saunders Elsevier; 2005. p. 119–21.

Behavior

Y. M. Awaad, *Absolute Pediatric Neurology*, https://doi.org/10.1007/978-3-319-78801-2_2

1. A 7-year-old and 9-year-old brothers, are being seen for their annual checkup by their PCP. The mother looks worn out and mentioned that her sons have always kept her busy. The younger brother has a lot of trouble with his school work. The mother said that he is smart, but he is not paying attention to anything, cannot concentrate for more than few minutes on his homework, is easily distractible, and never does what he is told, is constantly misplacing things, and even forgets to brush his teeth and shower sometimes if she does not remind him. The older brother also giving her trouble with his school work, he "just can't seem to sit still." At home, he is fidgety at the dinner table and while doing his homework. She was called several times to school because he leaves his seat and sometimes the classroom. He talks constantly, jumping from one topic to another, he does not wait his turn to answer, and is constantly butting into conversations.
   What is your most likely diagnosis?
   A. This is a normal age appropriate behavior.
   B. Generalized anxiety disorder
   C. Oppositional defiant disorder
   D. Attention-deficit/hyperactivity disorder
   E. Conduct disorder

Correct Answer is: D
They have the classic symptomatology of attention-deficit/ hyperactivity disorder (ADHD). ADHD includes a predominantly inattentive type, as in the younger brother; a predominantly hyperactive type, as in the older brother a combined type. The diagnostic criteria for the inattentive type include six or more symptoms of inattention that have been present for the prior 6 months with at least some symptoms occurring before age 7 years that are leading to functional impairment and are not consistent with developmental level and include failure to pay attention to details in schoolwork or other activities, difficulty sustaining attention on a task or activity, not listening when spoken to and not following instructions, difficulty with organization, avoidance or dislike of tasks that require sustained mental activity, loss of objects necessary for tasks or activities, easy distractibility, and forgetfulness in daily activities. The diagnostic criteria for the hyperactive type include six or more symptoms of hyperactivity and impulsivity that have been present for the prior 6 months with at least some symptoms occurring before age 7 years that are leading to functional impairment and are not consistent with the developmental level and include frequent fidgeting or squirming, leaving a seat in situations when remaining seated is expected, running about or climbing excessively in inappropriate situations, or feelings of restlessness, difficulty engaging quietly in leisurely activities, talking excessively, blurting out of answers, difficulty awaiting a turn, and interruption of others. Although the etiology of ADHD is not clear, dysfunction in frontal-subcortical circuits has been implicated. Genetic studies have suggested involvement of genes involved in dopamine action or metabolism, though environmental factors play a role as well. Children of parents with ADHD and siblings of children with ADHD are more likely to be affected with ADHD than the general population.

Oppositional defiant disorder is a distinct entity from ADHD, but the two are often comorbid. Similarly, generalized anxiety disorder is also comorbid with ADHD, as are the disruptive behavior disorders. In childhood, academic failure and peer rejection are the major consequences of ADHD, whereas in adolescence, there is a threefold increase in substance use and abuse. Approximately 60% of patients with ADHD in childhood continue to be impaired in adult life; ADHD may also not be recognized

until adulthood. Adults with ADHD typically show instability with employment and relationships. The first line of treatment for ADHD are psychostimulants, including amphetamines and methylphenidates, of which there are various oral preparations. Common side effects include reduced appetite, weight loss, insomnia, and headaches. An electrocardiogram prior to initiation of stimulant medications is recommended to exclude underlying structural or conduction problems.

2. An 8-year-old white boy came to your office for evaluation of developmental delay. Pregnancy was unremarkable and he was a full-term at birth. He was at the regular nursery for 2 days because he had a feeding problem and jaundice. He was 7 lbs. 8 oz. (25–50%ile) and length was 22 in. (>95%ile) at birth. On your examination, he is tall and macro-cephalic (both > 97th percentile) with mildly dysmorphic facial features, including a high, broad forehead, down-slanting palpebral fissures, and a pointed chin. His hands and feet are enlarged. The rest of his neurologic examination is normal. No other similarly affected individuals in the family.
Which genetic test would you like to order?
   A. Chromosome microarray
   B. FISH for chromosome 22q11 deletion
   C. Karyotype
   D. Methylation analysis of chromosome 15q
   E. Nuclear receptor SET domain containing protein-1 (NSD1 testing)

Correct Answer is: D
Sotos syndrome (cerebral gigantism), is a genetic condition affecting 1: 10,000 to 1: 50,000 individuals. It is characterized by prenatal and postnatal overgrowth, macrocephaly, and characteristic facial features—specifically a high anterior hair line; frontotemporal hair sparsity, a long, thin face; frontal bossing; down slanting palpebral fissures; and a prominent mandible. Advanced bone age is common but is not a universal finding. Hypotonia and global developmental delay is a neurologic hallmarks, however mild intellectual disability is present in the affected adults exhibiting. Sotos syndrome can be caused by either intragenic truncating mutations or microdeletions that result in haplo insufficiency of the nuclear receptor binding SET domain protein 1 (NSD1), located on chromosome 5q35.3. More than 80% accounts for intragenic mutations in European-origin white patients, on the other hand microdeletions has a higher incidence in the Japanese population. The majority of cases are sporadic, though autosomal dominant pedigrees have been reported.

Suggested Reading

Leventopoulos G, et al. A clinical study of Sotos syndrome patients with review of the literature. Pediatr Neurol. 2009;40:357–64.

3. A 7-year-old girl with a history of language difficulties. She was born full-term by normal spontaneous vaginal delivery following an uncomplicated pregnancy. Her milestones, walked at 10 months, said single words at 12 months, and combined words at 22 months. At age 5, her speech became progressively more telegraphic, and she started pointing or using sign language to indicate her needs. On your neurologic examination, she is able to follow simple commands. She has word-finding difficulties in spontaneous speech and on naming tasks and is unable to repeat short phrases. The rest of her neurologic examination is normal. Formal audiometric testing is normal.