16 The Neurological Perspective: Autism Spectrum Disorders and Other Developmental Disabilities

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Abstract

Neurologists provide valuable contributions to the care of children with autism spectrum disorders and other neurodevelopmental disorders, often addressing comorbid epilepsy and/or motor disorders. Children with ASD often have neurological comorbidities that are of utmost significance in addressing prognosis and treatment planning as well as informing research regarding the characterization of the autism spectrum disorder and the elucidation of ASD's underlying neural circuitry. The most common neurological abnormalities associated with ASD – stereotypies and praxis, motor deficits, epilepsy, gait and coordination, and sleeping abnormalities – are explored in this chapter. In addition the chapter explores recent neurological advances in unlocking the clues provided by these comorbidities to determine if they are specific to ASD and if they are causal in nature or an epiphenomena. The impact of recent advancements in the pathophysiology, epidemiology, and genetics of ASD spectrum on neurological interventions is explored, highlighting the hope for the better understanding and management of ASD through neurological research. Finally, this chapter details the manifestations of ASD along with evaluation and assessment from a neurological standpoint.

Keywords

Neurology · Autism · Epilepsy · Motor abnormalities · Genetics · Developmental disorders

Introduction

Neurodevelopmental disorders (NDD) are a heterogenous group of conditions featuring disturbances or delays in a variety of developmental domains including motor, cognition, language, and social faculties (Ismail & Shapiro, 2019; Jeste, 2015). The medical home team of children with NDD commonly includes a neurologist to lend expertise in nervous system development for assessment and treatment planning. This chapter will review the contribution of the neurologist to the care of children with neurodevelopmental disorders and comorbid epilepsy and/or motor disorders. After highlighting epilepsy and motor disorders generally, this chapter will discuss the care provided to children with autism spectrum disorder (ASD).

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ASD is a common, highly heritable neurodevelopmental disorder with a heterogenous presentation involving deficits in two major domains – social communication and reciprocity, and repetitive, restricted behaviors (Baumer & Spence, 2018). ASD prevalence has increased in the past few decades due to better recognition of the disease, broadening of the diagnostic criteria, as well as diagnostic substitution. There is a male preponderance with 4:1 male to female ratio (Christensen et al., 2016). The diagnosis of ASD is established with the contributions of medical home team members through taking a detailed developmental history from the parents and from observation of interaction between the child and the parents. Neurologists are commonly called upon to diagnose and appropriately manage neurological manifestations and comorbidities.

Epilepsy

The expertise of the pediatric neurologist is commonly sought for the identification and management of seizures in persons with developmental disorders. An increased incidence of epilepsy is found in many developmental disorders due to genetic, structural, and/or metabolic disturbances (Berg et al., 2017; Nickels et al., 2016). Genetic syndromes associated with epilepsy include Rett syndrome, Angelman syndrome, and fragile X syndrome (Berg et al., 2017). Tuberous sclerosis and neurofibromatosis are genetic disorders with a structural component contributing to epilepsy. Given the structural impact of cerebral palsy on the nervous system, the high prevalence of epilepsy in children with CP is not surprising nor is the fact that it can be particularly difficult to treat (Fiolita et al., 2020; Karatoprak et al., 2019). The prevalence estimates of epilepsy in children with ASD range from 4% to 38% (Lukmanji et al., 2019; Thomas et al., 2017). Epilepsy is diagnosed in persons with intellectual disability (ID) at a rate three to four times greater than the general population (Robertson et al., 2015).

Epilepsy co-occurs with ASDs with two peaks of onset, an initial peak that occurs in early childhood and a later peak in adolescence (Tuchman & Rapin, 2002). Conversely, ASD occurs in almost 46% of children with epilepsy (Matsuo et al., 2010). Coupled with the fact that children with intellectual and developmental disabilities (IDD) have an increased rate of comorbid ASD and epilepsy (Salpekar, 2018), patients with ASD may present to the neurologist for seizure evaluation at any age. Not surprising, with such medical complexity, seizure semiology is variable with complex partial, generalized, as well as mixed types being present – no single seizure semiology is most common (Jeste, 2011). A retrospective study involving 345 patients with ASD demonstrated 44% of paroxysmal abnormalities to be focal, 12% were generalized, and 42% were mixed (Parmeggiani et al., 2010). In this study, focal abnormalities were localized to temporal region in 31%, frontal in 18%, occipital in 13%, and parietal in 5% of the patients. A study of over a thousand Japanese children with ASD and epilepsy found more than 60% with frontal spikes, with significant involvement of the mirror neuron system which is known to contribute to symptoms of ASD (Yasuhara, 2010). A smaller retrospective study of 59 patients reported that seizures in the majority were found to be focal with or without secondary generalization (53.4%), generalized tonic-clonic in 19.2%, absence in 7.7%, polymorphic seizures in 4%, and preceding infantile spasms in 3% of the group (Pacheva et al., 2019). A British study of 150 children noted generalized tonic-clonic seizures to be the predominant seizure type (Bolton et al., 2011). In summary, the medical home team should be aware that seizure presentation is highly variable in children with ASD. See Table 16.1 for the seizure types associated with ASD in conformity with the International League Against Epilepsy (ILAE) classification scheme.

Risk factors for epilepsy in ASD include syndromic autism (Miles et al., 2005; Pavone et al., 2004), intellectual disability, and female sex (Amiet et al., 2008). Children with very early-onset seizures (e.g., infantile spasms) have an increased risk of ASD (Baumer & Spence, 2018). An important association exists between cognitive impairment and epilepsy in ASD (Ekinci et al., 2010) which is particularly robust in chil-

Table 16.1 Common seizure types in ASD/DD

Partial epilepsy/focal
Aware or impaired awareness
Motor onset
Non-motor onset
Generalized onset
Motor onset
Tonic-clonic
Other motor
Non-motor (absence)
Myoclonic epilepsy
Epileptic encephalopathies
Landau-Kleffner syndrome
Lennox-Gastaut syndrome
CSWS
West syndrome

dren with ASD in the context of tuberous sclerosis (Jeste et al., 2008). Even in the absence of epilepsy there is high prevalence of paroxysmal EEG abnormalities in ASD (Canitano, 2007; Jeste, 2011). A large retrospective study of children with ASD reported abnormal EEG discharges in 85% of the subjects, with the highest incidence of spikes in children with intellectual disability (Yasuhara, 2010). These paroxysmal EEG abnormalities could be either focal, generalized, or mixed with the focal abnormalities being mostly localized to the frontal lobe (Yasuhara, 2010). Given the prior finding of a significant incidence of spikes in children with intellectual disability, one could pose the question whether epileptic encephalopathy causes autism (Tharp, 2004). This is of relevance considering that pharmacotherapy aimed at spike suppression could potentially alter the developmental trajectory of patients with ASDs. The question being whether a pathophysiological association exists between epileptiform discharges and regression considering there is language regression seen in the setting of continuous slow wave spikes (Deonna & Roulet-Perez, 2010). More recent findings of the genetic overlap between ASD and epileptic encephalopathies add support to this possibility, but further research is necessary to fully understand this complex relationship (Srivastava & Sahin, 2017).

Pharmacological Management of Epilepsy

Management of epilepsy in ASD patients mostly follows the usual paradigm of epilepsy treatment. If a specific metabolic syndrome is found to be associated with the seizures in a patient with ASD, a specific treatment may be indicated. However, antiseizure mediations (ASMs) form the mainstay of treatment of epilepsy in ASD patients with the general treatment principles applied, although careful considerations should be made to minimize untoward behavioral side effects when choosing seizure medications due to the high rate of medical complexity in children with ASD and IDD. The common ASMs used for the management of epilepsy in ASD are reviewed in Table 16.2 including their most common side effects. Despite the frequent co-occurrence of seizures in ASD patients, there is relative dearth of studies evaluating effectiveness of ASMs (Frye et al., 2013). A survey conducted by the Autism Society of North Carolina with responders listing their medications as well as their satisfaction levels indicated that 15.2% of the individuals were receiving ASMs with the most common being carbamazepine, valproic acid, and phenytoin and the parents being satisfied in general with the ASM treatment (Aman et al., 1995). Of note, this study did not include newer ASMs including lamotrigine, lacosamide, and zonisamide, among others, that were not in common use or were approved after the study. Another survey study noted that valproate, lamotrigine, levetiracetam, and ethosuximide provided the best seizure control along with the least adverse effects among all the ASMs examined (Frye et al., 2011). As a general rule, newer ASMs such as lamotrigine, oxcarbazepine, topiramate, and levetiracetam have fewer side effects in comparison to older ASMs like phenobarbital, phenytoin, primidone, and carbamazepine. In our clinical experience, valproate, an older medication, has good efficacy for many patients with ASD. Potential side effects and spectrum of action are major considerations when prescribing an ASM. The broad-spectrum ASMs have effectiveness for a wide variety of seizures whereas narrow-spectrum ASMs are

Table 16.2 Antiseizure medications (ASMs) – spectrum and common adverse effects

AEDs	Spectrum of action	Adverse effects[a]
Valproate	Broad	Hepatotoxicity, hyperammonemia, weight gain, hair thinning, thrombocytopenia, and pancreatitis
Lamotrigine	Broad	Stevens-Johnson's syndrome (up-titrate slowly), abnormal liver function tests
Oxcarbazepine	Narrow	Hyponatremia
Levetiracetam (Keppra)	Broad	Behavioral side effects – agitation, aggression, and mood instability
Topiramate	Broad	Weight loss, psychomotor and cognitive slowing, metabolic acidosis, nephrolithiasis, and glaucoma
Lacosamide	Narrow	Dizziness, diplopia, and fatigue, precluded in abnormal heart rhythms
Carbamazepine	Narrow	Hyponatremia, dizziness, and ataxia
Zonisamide	Broad	Dizziness and loss of appetite
Ethosuximide	Narrow	Dizziness, nausea, vomiting, and sleep disturbance
Phenobarbital	Narrow	Drowsiness, lethargy, and hyperactivity
Phenytoin	Narrow	Abnormal liver function tests, gingival hyperplasia, ataxia, nystagmus, hirsutism, and coarsening of facial features
Clonazepam	Broad	Ataxia, cognitive dysfunction, and respiratory depression (rare)

[a]The US FDA (Food and Drug Administration) has issued a suicide risk warning on all ASMs. Note, most ASMs, if not all, are associated with detrimental effects on bone density/health aside from suicide risk

most applicable for focal, absence, or myoclonic seizures. While absence seizures – also called petit mal seizures – are generalized, focal onset seizure (previously known as partial seizure) means a seizure that occurs in a particular part of the brain. An ASM's side effect profile must be considered in relationship to the individual. For example, levetiracetam may exacerbate behavioral problems and is best avoided in children with behavioral abnormalities. Valproate is associated with weight gain and polycystic ovary disease limiting its use in girls and those with weight issues. Similarly, valproate is contraindicated in ASD patients with mitochondrial disorders as it may further impair mitochondrial functions. Valproate may increase abdominal distress in children with comorbid gastrointestinal disorders. This highlights the importance of communication between the patient, family, and medical team to fully understand each patient's unique challenges and needs.

Beyond the Pharmacological Management of Epilepsy

Non-epileptic treatments are typically used to treat seizures when ASMs are not effective. Multiple non-blinded and randomized controlled trials conducted in children showed effectiveness of ketogenic diet in epilepsy in children (Frye et al., 2013; Levy et al., 2012). In another retrospective case-control survey study, ketogenic diet was rated as the most favorable non-ASM treatment for improving seizures (Frye et al., 2011). In certain instances of patients with refractory epilepsy, particularly epileptic encephalopathies, intravenous immunoglobulin infusion and corticosteroids also have a role in treatment. In a retrospective review of 59 ASD patients with seizures who were treated with a vagus nerve stimulator (VNS), more than half experienced at least a 50% reduction in seizure frequency and significant improvement in the quality of life, suggesting a role of VNS in treatment of epilepsy in patients with ASD (Park, 2003). In cases where potential epileptogenic foci are visualized clearly with neuroimaging and identified as foci using various methodologies including magnetoencephalography (MEG), subdural intracranial recording grids, and/or intraoperative mapping, epilepsy surgery can also play a significant treat-

ment role. This is particularly true of patients with syndromic autism, for instance, tuberous sclerosis complex and tumors. These interventions can be frightening for children and their parents, necessitating multiple discussions and careful preparation of the child for the procedure.

Motor Disorders

The early identification of motor deficits is imperative for various reasons. Firstly, motor deficits are objective and quantifiable, providing a framework for measurement and a proposed role to act as motor biomarkers following temporal characterization and specificity studies in relation to NDD/ASD (Swanson & Hazlett, 2019; Thurm et al., 2016; Varcin & Nelson Iii, 2016). Second, motor deficits and the underlying neural circuitry dysfunction can enable classification schemes or endophenotypes within the heterogenous spectrum of NDD. And finally, motor function is critical in development, language acquisition, social interaction, and learning. Therefore, better characterization of motor deficits, including developmental coordination, stereotypic movement, and tic disorders and their precursors, can foster early intervention which could improve functional and behavioral outcomes for children with NDD.

Motor impairments are far less common in ASD compared to social communication and interaction despite being one of the earliest signs of ASD. Motor concerns include vestibular control impairment, gross and fine motor abnormalities, and oculomotor issues. Others such as motor clumsiness, delayed development of hand dominance, and primitive reflexes are nonspecific neurological symptoms associated with ASD (Mosconi & Sweeney, 2015). Interestingly, it has been suggested that motor deficit patterns may be able to distinguish ASD subtypes. Asperger's syndrome is characterized with consistent motor "clumsiness." ASD patients without language delays often demonstrate saccade dysmetria or abnormal eye movements. Given the frequency of motor impairments in genetic syndromes of autism (Geschwind, 2009) and that they generally do not improve over early childhood (Van Waelvelde et al., 2010), an important question remains regarding their role in the diagnostic process and inclusion in the diagnostic criteria of ASD.

Early oral-motor skills and imitation predict language acquisition in infants who are later diagnosed with ASD (Gernsbacher et al., 2008; McDuffie et al., 2005). A study analyzing motor function and gait from home videos of children with ASD, developmental delay and typical controls, showed that between groups, ASD children showed delayed development of movements including lying supine, sitting, and walking (Ozonoff et al., 2008). Other studies in the first 2 years of life showed delays in motor development including postural asymmetry, developmental milestones, and the overall gross and fine motor movements (Esposito et al., 2011; Iverson & Wozniak, 2007; Provost et al., 2007). A major limitation of these studies is the use of retrospective home videos without standardization. A prospective study also demonstrated low performance in gross and fine motor skills in the ASD group of children when examined at 24 months of age in comparison to language-delayed group within the study (Landa & Garrett-Mayer, 2006).

An entire plethora of gait abnormalities have been reported in children with ASD. A meta-analysis of 41 studies investigating coordination, gait, arm movements, and postural instability in ASD compared to controls showed significant motor incoordination and postural instability in the ASD group (Fournier et al., 2010). This is despite the heterogeneity in methodology of the various studies included in the meta-analysis. In a subgroup analysis, attenuation of effects with increasing age was seen suggestive of improved motor function over time. There are no strict guidelines as to when these abnormalities should be brought to a neurologist's attention; however, referral should be considered when impairment limits activities of daily living. As with other ASD comorbidities, there may be tremendous heterogeneity in presentation, and in most of the cases, there is attenuation of motor abnormalities over time.

Motor delays are common in many NDD, including fragile X, Down, Angelman, Noonan, and deletion 22q11 syndromes, cerebral palsy, muscular dystrophies, ADHD (attention deficit hyperactivity disorder), and ASD. The American Academy of Pediatrics has established guidelines for the early identification and evaluation of motor delays that include periodic screening at well-child visits and recommendation for physical examination and neuroimaging (Noritz & Murphy, 2013). The American Academy of Neurology details the screening and neuroimaging recommendations for children with cerebral palsy in a practice parameter (Ashwal et al., 2004).

Motor Disorders: Developmental Coordination Disorder/Dyspraxias

In neurology, *praxis* concerns the neural networks supporting the ability to produce both meaningful and meaningless gestures. Deficits in praxis, or dyspraxias, result in the impaired performance of the complex gestures that correlate with social, communication, and behavioral deficits with the early onset of dyspraxias affecting learning and overall cognitive development. For children with ASD, dyspraxia has been attributed to impaired formation of spatial representation and poor motor execution (Dowell et al., 2009; Dziuk et al., 2007; Mostofsky & Ewen, 2011).

When a dyspraxia interferes with activities of living and motor skills are substantially below expectations, a developmental coordination disorder (DCD) should be considered. The deficits in DCD may involve *planning, sensorimotor coordination, motivation, goal directedness, regulation of motor activities, and skill learning* (Fletcher et al., 2020, p. 173). DCD may be diagnosed in children with ASD if criteria are met; however, when assigning the diagnosis of DCD to a child with ID, the level of motor impairment must exceed that predicted by the ID alone (American Psychiatric Association & American Psychiatric Association. DSM-5 Task Force, 2013). There is limited prevalence data for DCD, with general estimates ranging from 2% to 20% (Blank et al., 2019). Preterm and low-birthweight children are at increased risk for DCD as are children with ASD and ADHD (Edwards et al., 2011; Kopp et al., 2010). Neurological assessment to rule out neuromuscular diseases, neoplasm, metabolic disorders, or other conditions that may cause coordination difficulties is indicated. A physical or occupational therapist may administer the Movement Assessment Battery for Children and the Bruininks-Oseretsky Test of Motor Proficiency and provide indicated therapy (Bruininks & Bruininks, 2005; Henderson, 1992). To offer further guidance, the European Academy of Childhood Disability has published clinical practice recommendations for the assessment and management of DCD (Blank et al., 2019).

Motor Disorders: Stereotypies

Stereotypic movements *are repetitive, seemingly driven, and apparently purposeless motor behaviors* (American Psychiatric Association & American Psychiatric Association. DSM-5 Task Force, 2013, p. 77). The DSM-5 (2103) instructs that self-injurious behavior and a known medical condition, such as neurodevelopmental disorder, should be noted as specifiers. A systematic review of stereotypies in persons with developmental disabilities involving 44 studies and representing 11,331 participants found an average prevalence of stereotypy of 61%. Diagnoses represented were Down, fragile X, Prader-Willi syndromes, and ASD, with stereotypy most common in persons with ASD, at 88% (Chebli et al., 2016). Significant stereotypical behaviors have also been reported in children with Angelman, Cornelia de Lange, Cri du Chat, fragile X, Lowe, and Smith-Magenis syndromes (Moss et al., 2009). For children with Cornelia de Lange and Lesch-Nyhan syndromes, stereotypical behaviors are often associated with self-injurious behavior (Nyhan, 1976; Srivastava et al., 2020).

Stereotypies should be assessed, and intervention considered when the movement:

(a) Persists at similar levels past the age of two
(b) Is displayed with high intensity or frequency

(c) Appears atypical or unusual in its manifestation
(d) Interferes with an individual's functioning (Chebli et al., 2016, p. 107) from Didden et al. (2012)

The earliest descriptions of ASD reported stereotypical behaviors (Asperger & Frith, 1991; Kanner, 1943). Motor stereotypies or repetitive behaviors often are present early in children with ASD and are intimately linked to social communication and cognitive deficit (low functioning, lower IQ ASD groups) and can correlate with disease progression and severity (Jeste, 2011). In the current DSM-5 classification, "stereotypies" are the only neurological manifestation included in the diagnostic criteria for ASD (American Psychiatric Association & American Psychiatric Association. DSM-5 Task Force, 2013). These abnormalities include finger movements, body posturing, rocking, spinning, hand/arm flapping, full-body testing, toe walking, and repetitive jumping, among others. Additionally, vocal stereotypies including repetitive sounds or verbal echolalia are common in ASD. A systematic review and meta-analysis involving 8124 persons with ASD found younger age, lower intelligence, and greater severity of ASD, but not gender, to be correlated with a higher number of stereotypies (Melo et al., 2020).

Sleep Disorders

Sleep is necessary for healthy neurodevelopment, and neurodevelopment influences sleep in a complex relationship (McKenna & Reiss, 2018). Variation in neurophysiology and/or neuroanatomy contributes to the high prevalence of sleep disorders in persons with developmental disorders (Esbensen & Schwichtenberg, 2016; Fletcher et al., 2020). Short sleep duration, low sleep quality/efficiency, and circadian sleep desynchronization are common in children with ASD as are behavioral challenges related to sleep (Carmassi et al., 2019; Mazurek & Sohl, 2016). For persons with ID, poor sleep quality and shorter duration are reported (Surtees et al., 2018). Sleep disorders are common in many genetic disorders including fragile X syndrome, tuberous sclerosis, neurofibromatosis, and syndromes including Down, Williams, Smith-Magenis, Rett, Prader-Willi, Angelman, and Lesch-Nyhan (Stores, 2014). Epilepsy may be associated with hypersomnia, insomnia, obstructive sleep apnea, restless legs syndrome, and parasomnias (Latreille et al., 2018). It is critical that the medical home team inquire directly about sleep as caregivers may underestimate the contribution of sleep disorders to behavioral challenges (Hoffmire et al., 2014). The impact of medication on sleep must also be considered by the team.

Sleep impairments are prevalent in a significant proportion of individuals with ASD and NDD. The primary disorder in ASD is insomnia, and there have been both subjective and objective measures investigating sleep disturbances with the prior employing questionnaires and the latter actigraphy and polysomnography. Subjectively, multiple studies have reported difficulty initiating and maintaining sleep, restless sleep, co-sleeping, and early morning awakenings (Jeste, 2011). Biologically, sleep impairment may be explained by aberrant circadian rhythms. Genes controlling circadian rhythms (clock genes) may have a role in modulating melatonin for sleep regulation and in integrity of synaptic transmission in ASD (Bourgeron, 2007; Nicholas et al., 2007). Other studies have suggested melatonin dysregulation (Tordjman et al., 2005) which is further corroborated by the finding of exogenous melatonin therapy being effective in improving sleep in ASD. Further studies plotting the developmental trajectory of sleep impairment prospectively are warranted to see if there are clinical associations of sleep impairments such as periodic limb movements and/or restless legs syndrome in children with ASD. Focusing and managing behavioral issues associated with ASD may have significant impact with sleep. More discussion on the sleep abnormalities associated with ASD can be found in the sleep chapter of this edition, Chap. 22.

Neurological Considerations in the Diagnosis of ASD

Screening for ASD

Considering the heterogeneity of ASD, most recommendations suggest multidisciplinary evaluation, medical evaluation, and genetic testing. There has been controversy with regard to universal screening for ASD with the US Preventive Services Task Force stating that not enough data were present to advocate for universal screening of children for autism (Baumer & Spence, 2018). However, the American Association of Pediatrics endorses recommendations for developmental surveillance and specific ASD screening at ages 18 and 24 months and for all children who fail routine developmental surveillance (Hyman et al., 2020a, 2020b).

The early neurological abnormalities seen with ASD are often peculiar and if investigated can facilitate both screening and diagnosis at an early age resulting in prompt intervention and treatment to promote a better prognosis. As discussed above the motor deficits seen in ASD correlate with the severity and are one of the earliest abnormalities linked with social and cognitive deficits (Jeste, 2011). In the current era, there is quite a need for further clarification and elucidation of the clinical and scientific evidence with empirical data which may help in a definite association between motor and cognitive skills in ASD.

As of now there are no motor impairments or neuroimaging signatures that are part of the diagnostic criteria of ASD. Considering that motor deficits are one of the common changes seen in ASD, future research is likely to modify the diagnostic criteria. Similarly, given the quantifiable nature of motor impairments, it could also be used as a biomarker and for characterization of endophenotypes of ASD which would facilitate early clinical interventions aimed at improving outcomes.

Clinical Evaluation of ASD Symptoms

Neurologists have a special role in the evaluation of patients with suspected ASD considering the attention to neurological details that is requisite for making the diagnosis. Evaluation of patients with suspected ASD includes detailed history, physical examination, and appropriate investigations. The medical history should include birth history, age of parents at birth (older paternal age being a risk factor for ASD), perinatal risk factors, and pregnancy or delivery complications. Clinicians should assess for medical conditions commonly seen in patients with ASD including gastrointestinal concerns, sleep disturbances, seizures/epilepsy, and lead exposure. Family history is also of importance including history of epilepsy, genetic, metabolic, autoimmune, speech, intellectual, and ADHD/learning disorders. Metabolic disorders should also be considered in the differential diagnosis and ruled out. Finally, the DSM-5 ASD diagnostic criteria including specific inquiry for social communication deficits and repetitive behavior/restricted interests must be evaluated.

A detailed physical and neurological examination of the patient is a significant part of evaluation. ASD is often associated with various neurogenetic syndromes. Therefore, assessment for dysmorphic features (e.g., prominent ears in fragile X syndrome or facial features suggestive of metabolic anomalies), growth parameters (height, weight, and head circumference), and skin examination to assess for neurocutaneous features (e.g., hypopigmented spots or fibromas) are pertinent. Neurologic exams emphasizing the patient's attention, cranial nerves, muscle tone, motor coordination, reflexes, and gait are all significant aspects of evaluation of patients with ASD.

Neurogenetic syndromes commonly occur in 10–20% of patients with ASD (Bourgeron, 2016). Children with fragile X syndrome, tuberous sclerosis complex, 15q duplication, neurofibromato-

sis, Angelman syndrome, Prader-Willi syndrome, Rett syndrome, and Down syndrome have increased rates of autism in comparison to general population (Johnson et al., 2007). Chromosomal microarray testing is useful for detecting copy number variations, but in order to diagnose balanced translocations, whole exome sequencing (WES) or whole genome sequencing (WGS) may be needed. To identify genetic aberrations involving single nucleotide polymorphisms, WES/WGS is required (Sanchez Fernandez et al., 2019; Shendure et al., 2004).

Depending on the clinical phenotype, further investigations including brain MRI, EEG, and metabolic testing must be considered. The relevance and implications of neuroimaging and electroencephalography are detailed below. Neuroimaging is particularly useful in situations where there is microcephaly, hypertonia, and focal neurological deficit(s) or when concern for neurodegenerative disease process is a consideration. Often, neuroimaging may help in excluding cortical dysplasia, mesial temporal sclerosis, and cystic lesions which have been associated with ASD (Casanova et al., 2013). In cases where there are concerns for clinical or subclinical seizures, an EEG should be considered. EEG is also necessary in instances where regression is secondary to possible Landau-Kleffner syndrome or in cases of acquired epileptic aphasia. In situations where a metabolic defect is suspected, varied tests including plasma and urine amino acids, plasma acylcarnitine, and even checking lead levels should be considered. Audiologic testing is also important in children with language delay and diagnosis of ASD since it may be a treatable condition.

A framework for the evaluation of ASD from a neurological perspective with management options is presented in Table 16.4. The evaluation and management of ASD is best accomplished through a multidisciplinary approach including neurologists and other specialists as indicated. The medical home approach enables the needs of the child and family to be addressed in a comprehensive manner.

Neurobiology: Insights from MRI Findings and Electrophysiologic Studies

Neuroimaging

MRI is a useful imaging modality which can facilitate understanding of how the brain develops structurally and functionally in patients with ASD when compared to controls. Reproducibility of results is an issue to date, primarily due to motion artifacts (Power et al., 2019) and/or different scanning machines. However, structural studies employing diffusion tensor imaging (DTI) (Solso et al., 2016) and functional MRI (fMRI) (Clements et al., 2018) have enhanced our understanding of how altered neural circuits relate to the clinical syndrome of autism (Ecker et al., 2012; Langen et al., 2014). MRI studies support the heterogeneity of autism, demonstrating various subgroups with different neurobiological alterations to explain the symptomatology. Longitudinal studies with multiple brain MRIs of infants at high risk of developing autism during their first 2 years of life have detailed the structural changes associated with autism (Wolff et al., 2012). The current studies suggest the presence of disruption of neural pathways prior to the emergence of behavioral symptoms in autism which might help regarding the underlying mechanisms. The data from MRI studies has revealed differences in the neurobiology between young children diagnosed with autism and those without, specifically, differences in cortical thickness decrease in regions involving language, social cognition, and behavioral control (Smith et al., 2016). A major obstacle in using neuroimaging with MRI as a reliable biomarker in patients with autism is reproducibility (Uddin et al., 2017).

Language production and comprehension are the core features affected in autism. fMRI studies investigating circuits for language have demonstrated hyper-activation of the superior temporal gyrus and inferior frontal gyrus as well as hypo-activation of the bilateral middle temporal gyri (Emerson et al., 2017; Herringshaw et al., 2016).

In addition, these studies have identified correlates for challenges in processing emotions shown by faces and the "social brain" and deficits in attention (Herringshaw et al., 2016).

As research in this area progresses, MRI studies could be well suited to categorize subgroups of autism (Lombardo et al., 2015) as well as in differentiating from other neurodevelopmental anomalies (Carlisi et al., 2017). The use of MRI as a biomarker in response to treatments and for purposes of longitudinal tracking currently remains in its infancy.

Electrophysiological Studies

Traditionally, EEG has been used to diagnose comorbid epilepsy in patients with ASD (Levisohn, 2007) although it can also be used to study its mechanisms. EEGs have the benefit of being less expensive than MRIs, making the study of brain dynamics on a smaller timescale more economically feasible. Like EEG, magnetoencephalography (MEG) is noninvasive and records the activity of the brain surface; however, MEG provides higher spatial resolution than EEG. Both have been used to explore brain connectivity in persons with ASD, noting a more random connectivity pattern overall (O'Reilly et al., 2017).

EEG has revealed alterations in oscillatory activity in resting state in autism patients, with more slow waves, less alpha waves, and less intra- and interhemispheric asymmetry than in normal controls (Cantor et al., 1986). Parsing out endophenotypes of ASD using spatiospectral analyses to map out trajectories of EEG in infants is an application in development (Lefebvre et al., 2018; Tierney et al., 2012). Other studies focusing on mechanisms have used task-based modulation of cognitive faculties – examples being low-level perception and action observation – in people with ASD. A feature of ASD involves failure to mirror an observed action of another person (Chan & Han, 2020) which was based on altered mu wave suppression in autism (Oberman et al., 2005) previously but later was questioned empirically (Bernier et al., 2013). This implies a more complex picture of impaired executive functions and visual attention (Dumas et al., 2014). Additional studies have shown modulation of sensory processing in people with autism with observed changes in sensitivities and latency (Marco et al., 2011). It is also important to note here that interactive tasks that encompass real-time social interaction would allow study of brain activity in experimental contexts that would be more relevant to autistic symptoms than passive tasks which are used for most functional imaging studies.

Management

The management of patients with ASD involves multiple approaches including behavioral and educational therapies apart from addressing comorbidities (Table 16.3). For educational purposes, agencies in the United States, including the Centers for Disease Control and Prevention, the National Institutes of Health, and private foundations and groups (e.g., Autism Speaks, Autism Society of America, and American Academy of Pediatrics), have multiple resources

Table 16.3 Neurological management of ASD/DD

Neurological interventions
Neurological evaluation
Family education
Management of epilepsy
Antiseizure medications
Vagus nerve stimulator
Ketogenic diet
Other interventions
Steroids
IVIG (intravenous immune globulin)
Refer to medical home team for treatment
ASD – ABA, speech/language, OT, PT, etc.
Comorbid conditions – ID, mental health, etc.
Sleep hygiene
Future directions
Syndromic autism – Fragile X syndrome, Rett syndrome, Angelman syndrome, Prader-Willi syndrome
New avenues including gene editing
CRISPR/Cas9 modality
ASOs

Table 16.4 The neurologist's clinical approach to ASD

Detailed history	Detailed physical examination	Further testing
Birth history Age of parents at birth Perinatal risk factors Pregnancy complications Comorbid conditions Epilepsy/seizures Intermittent explosive disorder Motor impairments Developmental history Family history Metabolic disorders ADHD/learning disorders	Complete neurological exam (esp. checking for UMN (upper motor neuron) signs) Dysmorphic features Growth parameters Neurocutaneous examination Evaluate for social communication deficits and restrictive/repetitive domains	MRI (magnetic resonance imaging) Electroencephalography Video EEG (to evaluate seizure – like activities, that is, motor stereotypies and tics) Serum and urine testing for metabolic disorders Audiologic testing Genetic: Chromosomal microarray Fragile X WES – whole exome sequencing WGS – whole genome sequencing Metabolic disorder testing if warranted

to help the patients and their families affected with ASD. It is widely recognized that intensive early interventions for children with ASD lead to improved long-term outcomes and greater skill development (Dawson et al., 2010; Reichow, 2012). Applied behavior analysis (ABA) is currently considered the gold standard treatment for ASD based on learning skills and repetition and reinforcement to obviate maladaptive behaviors. ABA can be used to improve cognition, adaptive behaviors, communication skills, and socialization (Dawson et al., 2010; Reichow, 2012; Schreibman et al., 2015).

Neurologists assist with assessment and management of the motor impairments and epilepsy associated with ASD. Additionally, as discussed earlier, diagnosis and identification of neurogenetic syndromes associated with ASD can be managed with the assistance of a neurologist. For example, the continuous spikes and waves during sleep (CSWS) can masquerade as ASD (Tuchman, 2009). Treatment with high-dose nightly diazepam has been used for CSWS (Sanchez Fernandez et al., 2014). In addition, Landau-Kleffner syndrome (LKS), characterized by epileptic aphasia, clinical seizures, and abnormal EEG findings, can be misdiagnosed as autistic behavior. It is imperative to have clinical suspicion for LKS considering the imperative to prevent epileptic regression and start therapy including ASMs, nightly benzodiazepines, and corticosteroids (Frye et al., 2013; Tuchman, 2009). For epilepsy/seizures in patients with ASD, ASMs are prescribed by neurologists. Levetiracetam is often avoided in autistic patients with psychiatric comorbidities due to an association with depression and thoughts or self-harm. Depakote and Lamotrigine are more commonly used in persons with ASD (Frye et al., 2013).

Psychiatric and behavioral comorbidities are common with ASD. Cognitive behavioral therapy (CBT) has been shown to be beneficial for anxiety in high-functioning children with autism (Danial & Wood, 2013). Atypical antipsychotics, including risperidone and aripiprazole, have been FDA approved for treating aggression and irritability in children with ASD (Baumer & Spence, 2018). For ADHD, non-stimulant medications including norepinephrine reuptake inhibitors (atomoxetine) and α_2-adrenergic agonists (guanfacine and clonidine) are commonly used (Jain et al., 2011; Jeste, 2015; Kratochvil et al., 2002; Sallee et al., 2009). For anxiety or OCD (obsessive-compulsive disorder) coexisting with ASD, selective serotonin reuptake inhibitors (SSRIs) have been used with success (Baumer &

Spence, 2018). Note though, particular attention needs to be given in using tricyclic antidepressants (TCAs) and bupropion in patients with ASD, given their propensity to decrease the seizure threshold. For a more nuanced discussion of the role of the psychiatrist in caring for children with ASD and IDD, see Chap. 19 in this volume.

Various other treatments including dietary modifications, vitamin supplementation, acupuncture, chiropractic, chelation, hyperbaric oxygen, and immunologic agents have been used in ASD patients although inadequate scientific evidence exists to support these treatments (Levy & Hyman, 2015). Previously, there had been controversy regarding vaccinations and increased risk for ASD. Subsequent studies and CDC guidelines unequivocally negate any links between vaccination and ASD risk (Institute of Medicine, 2004).

Future Directions

With recent advancements in the genetic toolkit, neurologists are poised to develop new therapeutic strategies for ASD particularly for children with monogenic autism. Antisense oligonucleotides (ASOs) have recently been used for early-onset neurological disorders like spinal muscular atrophy (Mendell et al., 2017). For ASD resulting from high-confidence risk genes, ASOs may provide hope. Similarly, CRISPR/Cas9 as gene-editing technology may offer new approaches to treatment as our knowledge of ASD expands, providing more specific targets (Zhao et al., 2018). As science unravels these mysteries, neurologists will have new tools for the evaluation and treatment of ASD and other NDD, advancing the ability of the medical home team to enhance the quality of life for children.

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