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The Neurology of Autism Spectrum Disorders

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Abstract

Purpose of review—Neurological comorbidities in autism spectrum disorders (ASD) are not only common, but they are also associated with more clinical severity. This review highlights the most recent literature on three of autism’s most prevalent neurological comorbidities: motor impairment, sleep disorders, and epilepsy.

Recent findings—Motor impairment in ASD manifests as both delays and deficits, with delays found in gross and fine motor domains and deficits found in praxis, coordination, and gait, all of which affect other cognitive and behavioral domains. Sleep disorders, especially insomnia, occur in up to 83% of children with ASD and recent studies have begun to explore the underlying biochemical and behavioral basis of the impairment, which has bolstered treatment studies. Epilepsy is reported in up to one-third of children with ASD, and new studies have focused on identifying the genetic causes of this association.

Summary—Better characterization of the phenotype, developmental trajectory, and underlying pathophysiology of these neurological comorbidities will enable us to define neurological endophenotypes within the autism spectrum. Future studies must investigate the emergence of these comorbidities prospectively in order to determine whether they lie on the causal pathway to ASD or whether they reflect epiphenomena of the disorder. Since epilepsy and sleep disorders can be treated and may contribute significantly to behavioral and cognitive abnormalities in ASD, their identification is of high clinical relevance.

Keywords
autism; neurology; motor; sleep; epilepsy; endophenotype

Introduction

The relevance of autism spectrum disorders (ASD) to the field of neurology has a rich history, but recently there has been a growing focus on neurological comorbidities in ASD and their implications for prognosis, treatment, and the elucidation of aberrant underlying neural circuitry. In this review, I will discuss three neurological comorbidities: motor impairment, sleep disorders, and epilepsy. To be considered throughout the review are the following: (1) Are these impairments specific to ASD? (2) Do they lie on the causal pathway to ASD or do they reflect epiphenomenon of the disorder? (3) What is the timing and developmental trajectory of these domains?
Motor impairment

The appreciation of motor impairments in ASD dates back decades. In 1978 and 1982, Antonio Damasio and Ralph Maurer wrote seminal papers in *Archives of Neurology* and *Journal of Autism and Developmental Disorders* addressing this issue. Applying a localization model to their clinical examinations, they argued that the motor deficits seen in children with autism pointed to a dysfunction in specific cortical and subcortical structures, particularly mesolimbic cortex and fronto-striatal circuits.[1,2]

Since then, a wide range of motor delays and deficits has been reported in ASD, although only repetitive behaviors are included in the diagnostic criteria. Delays occur in both gross and fine motor domains, while deficits are documented in praxis, motor planning, gait, coordination and postural control. A recent study has demonstrated that these deficits do not improve over early childhood in ASD. [3•] Nearly 90% of genetic syndromes associated with autism have significant motor impairment. [4] Given their prevalence, a key question is whether motor impairments should be considered a core deficit of the disorder.[5] There are several reasons that motor impairments warrant investigation. First, motor signs are highly quantifiable and can be objectively measured. Second, these deficits and delays may shed light on clinical endophenotypes within the heterogeneous spectrum. Third, recognition of motor anomalies may guide the definition of underlying aberrant neural circuits leading to ASD. Fourth, motor function is critical for broader aspects of development, including language, social interaction and learning, and therefore a better characterization and early identification of motor abnormalities may facilitate interventions that could improve functional and behavioral outcomes. Finally, by investigating the timing of motor impairments and their specificity to ASD, we may identify motor markers that facilitate earlier diagnosis of ASD. A major challenge lies in the development of developmentally appropriate assessment tools and standardized scales to quantify and characterize motor impairment, particularly in young children and infants. As a result, most studies focus on older or higher functioning children with ASD.

Motor delay

The identification of early motor deficits holds particular clinical relevance, as early oral-motor skills and motor imitation have been shown to predict language acquisition in infants with ASD[6–9]. In a recent study, Ozonoff et al. analyzed gross motor function and gait from home videos of children with ASD, developmental delay (DD) and typical controls in the first year of life, and then performed motor assessments after diagnosis. They found that growth trajectories of motor skills differed between the groups, with the ASD children demonstrating delayed development of movements, including lying supine, sitting, and walking.[10] Several other studies have documented delays in motor development in the first two years of life, including significant postural asymmetry in first unsupported gait,[11•] onset of early developmental milestones, less time spent in certain gross motor postures,[12] and overall gross or fine motor delay.[13] One limitation to these infant studies is the use of retrospective home video, which inevitably lacks standardization. However, the findings lay a promising foundation for prospective studies of infants at risk for ASD.

Repetitive behaviors

The only motor deficit included in the diagnostic criteria for ASD is the presence of repetitive behaviors, or stereotypies. While traditionally viewed as “self-stimulatory,” there has been a growing appreciation for the fact that these likely represent an involuntary movement disorder. Several recent studies have carefully analyzed this domain to characterize subtypes and phenotypic correlates. The most comprehensive study was performed by Goldman and Rapin, which used video data to quantify and characterize...
stereotypies in a large sample of children ages 2–11 with ASD, IQ matched DD children, and typical controls. [14••] Prevalence of stereotypies was highest in the low functioning ASD group (70%), followed by 63% in the high functioning ASD group, 30% in the low IQ DD group, and 18% in the higher IQ DD group. Children with ASD had the greatest variety of repetitive behaviors, and behaviors most specific to ASD were hand/finger and gait stereotypies. The authors suggest that these findings support aberrant cerebellar as well as fronto-striatal circuitry that may be specific to ASD, particularly ASD with comorbid cognitive impairment. Supporting the association of repetitive behaviors with more severe phenotype, Lam et al found that repetitive movements were associated with lower IQ and more impaired social and communication domains, while Loftin et al demonstrated that social skills intervention improves repetitive behaviors.[15,16] These studies support not only the specificity of repetitive behaviors for ASD, but also suggest that clinical severity may be predicted by their presence. Two areas in need of further investigation are the mechanism underlying the relationship between cognitive impairment and stereotypies, and the distinction between the repetitive movements seen in other neurobehavioral disorders, such as Tourette syndrome, and those found in ASD. Both areas of investigation would facilitate our understanding of the aberrant neural circuitry underlying these movements and provide greater specificity to the impairments seen in ASD.

Praxis

Mostofsky and colleagues have investigated the performance of skilled movements in high functioning children with ASD using a praxis examination including gestures to command, imitation, and tool-use. They have documented impairments in praxis in all domains compared to IQ matched controls. Importantly, they have also found that dyspraxia is significantly correlated to social, communication and behavioral deficits.[17,18] Through an elegant study investigating the subcomponents of praxis, the group postulates that the dyspraxia is rooted in impaired formation of spatial representation and poor motor execution.[19•] While the children in these studies were all high functioning, Green et al investigated children with a wide range of IQ’s, ages 11–14, and found that skilled movement impairments were most prominent in children with IQ < 70. Green concludes that the presence of these praxis deficits may reflect overall severe neurological impairment. [20] However, it is also possible that early skilled movement deficits affect learning and cognitive gain, thereby causing the cognitive impairment.

Gait and coordination

Gait abnormalities have been extensively reported in children with ASD, including toe-walking, ataxia, variable stride length and duration, incoordination, postural abnormalities in the head and trunk, reduced plantarflexion and increased dorsiflexion.[21–25] In 2010, Fournier et al published a meta-analysis of 41 studies investigating coordination, gait, arm movements and postural stability in ASD compared to typical controls. Despite the tremendous heterogeneity across studies in assessment tools and participant characteristics, the authors found significantly more motor incoordination and postural instability in the ASD group. In subgroup analyses, this difference was found regardless of diagnostic category (ASD, autism, Asperger’s), with an attenuation of effects with increasing age, suggesting improved motor function over time.[26••] The authors did not have enough data on IQ to investigate the relationship between cognitive function and incoordination.

Neural basis for deficits

Most of the early hypotheses about the aberrant neural circuitry causing motor impairments were based on clinical reasoning and localization, with cerebellar and fronto-striatal circuits often implicated.[24,27] Recently, however, several neuroimaging studies have directly investigated the neuroanatomical basis for motor deficits. Mostofsky et al found that in 8–12
year old children with ASD, increased left motor cortex and pre-motor cortical white matter volumes were predictive of poor motor performance on the Physical and Neurological Subtle Signs (PANESS). In comparison, typical controls showed a positive correlation between white matter and motor performance, while children with ADHD showed no correlation.[28] The same group performed an fMRI investigation of basic sequence finger tapping in children with high functioning autism and age matched controls and found that, although performance did not differ, the ASD group showed reduced activation in a variety of cerebellar regions and also decreased functional connectivity between cerebellar and cortical regions.”[29•] Finally, using volumetric MRI, the same group found that abnormalities in basal ganglia shape predicted impaired praxis and motor skill in children with ASD.[30•]

**Future directions**

Clearly motor deficits are prevalent in ASD, and certain types of deficits may be specific to the disorder. It also has been shown that motor impairment may correlate to more severe phenotype, thus holding important clinical implications. The pathophysiology and timing of the relationship between cognitive impairment and motor impairment warrants investigation. Building on this promising work, future studies need to investigate motor function in infants at risk for ASD and in young children at the time of diagnosis, and to then correlate these findings with longer-term outcomes. Comprehensive neurological scales need to be developed for infants and toddlers in order to isolate delays and deficits in a standardized manner.

**Sleep disorders**

Sleep impairments range from 44 to 83% depending on the target population, assessment tools, and definition of sleep impairment. [31] Sleep disorders are reported to be more common in ASD than in other childhood neuropsychiatric disorders, such as ADHD, anxiety, and developmental delay. [32] The primary sleep disorder in ASD is insomnia. Two primary modes of investigation of sleep are used: “subjective” measures through parent questionnaires and sleep diaries and “objective” measures using actigraphy and polysomnography (PSG). Although better tolerated than PSG, there is some concern that actigraphy may under report sleep problems. [33,34,35,••36,37]

**Subjective measures**

Caregivers report difficulty initiating and maintaining sleep, restless sleep, co-sleeping and early morning awakenings.[38–42] Most studies use the Children’s Sleep Habits Questionnaire (CSHQ), although recently Malow and colleagues developed the Family Inventory of Sleep Habits as an alternative measure of sleep hygiene. [42] Parents of children with ASD also report greater sleep problems than parents of typically developing children, evidence of a broader sleep phenotype in ASD.[43•] In order to better define the specificity of sleep impairment in children with ASD, several behavioral studies have compared children with ASD to children with DD and have found higher rates in the ASD group (53% ASD s. 46% DD).[40,41] In a comparison of ASD to Down syndrome, Prader-Willi syndrome, and typical controls, ASD children showed settling difficulties and co-sleeping, whereas excessive daytime sleepiness characterized and differentiated the children with Prader-Wili Syndrome. [41]

**Objective measures**

Most studies use objective measures to confirm the presence of insomnia in children with ASD. Buckley et al recently published a comprehensive PSG study in which they measured overnight recordings in children ages 2–13 with ASD, IQ matched DD, and typical controls.
Etiology

Both behavioral and biological mechanisms have been implicated in the etiology of sleep impairment, and likely it is the interplay of both factors that drives these impairments. Behaviorally, abnormal sleep hygiene is commonly reported, with maladaptive bedtime routines causing challenges for parents in limit setting and appropriate sleep onset. The biological basis for sleep impairment may lie in aberrant circadian rhythms.[50] Two recent papers have proposed that genes controlling circadian rhythms (“clock genes”) may be implicated in the modulation of melatonin for sleep regulation and, perhaps, in the integrity of synaptic transmission in ASD. [51,52] Others have proposed melatonin dysregulation in ASD[53,54], further supported by the fact that exogenous melatonin therapy can improve sleep in these children. In a recent study, Melke et al suggested that the N-Acetylserotonin O-methyltransferase (ASMT) gene, which encodes the final enzyme needed for melatonin synthesis, is less active in individuals with ASD, leading to lower levels of melatonin. [55]

Associated clinical factors and prognosis

In the last several years, studies have demonstrated that sleep impairment is associated with more clinical comorbidities. In 2009, Goldman and Malow published a comprehensive study using parental report (CSHQ), actigraphy and polysomnography to characterize 42 children, ages 4–10, with ASD and 16 age-matched, typical controls. Children were classified as either “good sleepers” or “poor sleepers” based on parent report, with phenotypes were supported by PSG. Poor sleepers with ASD showed more hyperactivity and greater restricted/repetitive behaviors than good sleepers.[35] Other recent studies have found sleep impairment to correlate to hypersensitivity, epilepsy, ADHD, medication use and mood disorders.[39,56] Several recent studies have also demonstrated an association between epilepsy and sleep impairment, suggesting a common dysfunction in neuronal circuitry.[57] However, the directionality of the relationship remains to be elucidated, which would best be accomplished through prospective, longitudinal studies.

Treatment

Fueled by the growing appreciation for the prevalence and clinical comorbidities of sleep impairment, and the greater understanding of etiology, there has been a rise in intervention studies, both behavioral and pharmacologic, with particular focus on melatonin. Behavioral interventions focus on parent education, particularly around nighttime routines and sleep hygiene.[58,59] Reed et al recently designed a small group parent education workshop surrounding sleep hygiene for children ages 3–10 with ASD and demonstrated improvements in both actigraphy and CSHQ scores.[60]

While melatonin has been used clinically for years in children with an ASD, the earliest studies were either case-series or retrospective.[61,62] In the largest retrospective review of 107 children, published by Andresen et al in 2008, investigators found that 25% of children reported no sleep problems after treatment with melatonin, and another 60% reporting partial improvement.[63] The largest randomized controlled trial of melatonin was published in 2010. Twenty-two children with ASD ages 3–16 were randomized to melatonin or placebo and treated for 3 months. Melatonin dose was titrated for effect to a maximum dose of 10 mg. Based on questionnaires and sleep diaries, melatonin was found to improve sleep latency and total sleep time, but did not improve number of nighttime awakenings.
Importantly, children who showed improved sleep also showed a reduction in daytime behavioral difficulties, such as disruptive behavior, anxiety and social impairment. A smaller randomized controlled trial investigated efficacy in children with Fragile X and ASD and found that 3 mg of melatonin improved sleep-onset and sleep duration in this population. These very promising studies support the contention that treatment can be very effective for sleep, which, in turn can improve overall clinical status. The next step will be to characterize the clinical phenotype of the children who do respond to specific treatments in order to better target interventions to more homogeneous subgroups.

Future directions

The recent literature has clearly demonstrated the prevalence and nature of sleep impairments in ASD, with emphasis on the association of sleep impairment with other clinical comorbidities. Building on these studies, it will be important to investigate the developmental trajectory of sleep impairment, as can only be done through prospective studies. Furthermore, studies need to examine the impact on sleep impairment on specific cognitive domains, such as memory and procedural learning, founded on the rich literature on the negative impact of sleep deprivation on cognition in adults, as this would have tremendous implications for clinical outcomes in these children.

Epilepsy and Epileptiform EEG’s

The presence of epilepsy in ASD has been known since Kanner’s first reported cases in 1943. In the past several years there has been a growing interest in the mechanism by which the two co-occur and the insight into the etiology of ASD that can be gained by understanding the role of epilepsy in the disorder. Three outstanding reviews have been written by child neurologists (Spence, Tuchman, Brooks-Kayal) in the past year that addressing the relationship between ASD, epilepsy, and epileptiform EEGs.  

Clinical Characteristics

The prevalence of epilepsy in ASD is approximately 30%, with reported rates ranging based on the demographics of the populations studied. There are two peaks in the age of epilepsy onset, the first in early childhood and second in adolescence Conversely, ASD occurs in up to 46% of children with epilepsy. No single seizure semiology is most common, with studies reporting complex partial, generalized and mixed seizures types. There is a very clear association between cognitive impairment and epilepsy in ASD.  

The incidence of paroxysmal EEG abnormalities in ASD is even higher than epilepsy. A recent large retrospective study of 1014 children with ASD reported abnormal EEG discharges in 85% of children, with the highest incidence of spikes in children with intellectual disability. As in epilepsy, there is not one common epileptiform pattern associated with ASD. A study of 345 inpatients with ASD found that 44% of paroxysmal abnormalities were focal, 12% generalized and 42% mixed. Focal abnormalities were localized to temporal regions in 31%, frontal in 18%, occipital in 13% and parietal in 5%. However, the Yasuhara study described above found that more than 60% had frontal spikes. The association between paroxysmal abnormalities and phenotype is one that has been deeply investigated by researchers, and in a recent review, Barry Tharp articulated the critical question: “Do spikes cause autism?” This question holds particular relevance to the potential for pharmacotherapy aimed at spike suppression to alter the developmental trajectory that would otherwise lead to ASD. An associated question is whether there is a pathophysiological association between epileptiform discharges and regression, particularly
given the clear clinical phenotype of language regression in the setting of continuous slow wave spikes (CSWS)[80]. Tharp concludes that there is no clear evidence that epileptiform discharges usually cause the phenotype of ASD and, therefore, no support for using antiepileptics to “treat” or prevent ASD. From a clinical standpoint, while there is no doubt that frank seizures should be treated, the challenge lies in making the distinction between epileptiform discharges and epilepsy in these children who are often difficult to characterize. The question remains, short of performing routine EEG surveillance of every child with an ASD, how best can clinicians accurately make the diagnosis of epilepsy?

Pathophysiology

It has been proposed by several investigators that both epilepsy and ASD reflect aberrant connectivity and disordered synaptic plasticity (for a comprehensive review, see Brooks Kayal, 2010 [69••]). This hypothesis finds support from several recent genetics studies, which have found copy number variants (CNV’s) in 8–10% of individuals with idiopathic epilepsy, most commonly in genes implicated in synaptic integrity and, importantly, in neurodevelopmental disorders. Such CNV’s include CNTNAP2, 15q11.2, 15q13.3 and 16p13.11, and CDKL5.[81,•82,83,•84] From a neuroanatomic standpoint, it has been proposed that both epilepsy and ASD reflect aberrant connectivity, both long and short range.[85–87] The developmental trajectory of this “dysconnection” and the causative role of epilepsy in neurodevelopmental impairment has not been elucidated, partly because, as in our discussion of both motor and sleep impairments, there have been no prospective studies investigating both EEG and neurobehavioral phenotypes in infants prior to formal diagnoses. However, in infants with TSC, early onset seizures and, specifically, infantile spasms, significantly correlate with neurodevelopmental impairment.[88]

Treatment

Currently, no single anti-epileptic medication is found to be more effective for children with epilepsy and ASD.[89] Were we better able to elucidate the developmental course and pathophysiological relationship between epilepsy and ASD we would better be able to design therapeutics that could potentially treat not simply the epilepsy or abnormal EEG, but also alter the pathway to ASD. Furthermore, studies have not formally investigated the role of spike suppression in neurocognitive outcomes in children with idiopathic ASD, although a recent study performed in TSC demonstrated improved cognitive and behavioral outcomes when seizures were controlled early in life. This study was particularly striking because none of the children achieving early seizure control with Vigabatrin developed ASD, compared to 50% in the comparison group.[90••]

Future directions

Through the advances of the last several years, we now can explore the relationship between specific EEG characteristics and behavioral and cognitive profiles, and then use our knowledge of genetics and molecular mechanisms to better understand the relationship between epilepsy and ASD. Furthermore, as discussed in prior sections, studies of infants at risk will enable us to understand the time course of EEG abnormalities and their impact on aberrant development.

Conclusion

Neurological comorbidities such as motor dysfunction, sleep impairment and epilepsy are not only prevalent in ASD, but also associated with a more severe phenotype. Prospective studies will allow us to understand the etiology and temporal relationship of this association. Furthermore, as we continue to explore the neurobiological and genetic bases of these domains, we may be able to use the neurology of ASD to disentangle the heterogeneity of
this disorder and, importantly, gain insight into clinical endophenotypes within the spectrum. Lastly, these comorbidities offer excellent windows for treatment and clinical improvement, as even in the absence of ASD, they lead to significant impairment when untreated.

Key points

1. Neurological comorbidities are common in ASD and are associated with more severe phenotype, therefore warranting attention.
2. Motor impairment includes both developmental delays and deficits, include stereotypes, dyspraxia, incoordination and gait impairments, and are often associated with cognitive impairment.
3. Sleep disorders, particularly insomnia, occur in up to 83% of children and are likely reflective of abnormalities in circadian rhythms and melatonin regulation.
4. Epilepsy and epileptiform EEG’s occur in up to 50% of children and may reflect aberrant synaptic development and plasticity.
5. Better characterization of these comorbidities and their underlying pathophysiology will facilitate the definition of neurological endophenotypes within the autism spectrum.

Acknowledgments

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53. Leu RM, Beyderman L, Botzolakis EJ, Surdyka K, Wang L, Malow BA. Relation of Melatonin to Sleep Architecture in Children with Autism. J Autism Dev Disord. 2010 This is the first study to investigate the relationship between melatonin levels and sleep architecture (via PSG) in children with ASD, and it holds important implications for treatment.


64. Wright B, Sims D, Smart S, et al. Melatonin Versus Placebo in Children with Autism Spectrum Conditions and Severe Sleep Problems Not Amenable to Behaviour Management Strategies: A Randomised Controlled Crossover Trial. J Autism Dev Disord. 2010 This is one of few, and largest, randomized controlled trials of the use of melatonin for sleep disorders and it finds a significant improvement in sleep with melatonin. It also isolates the specific sleep domains that improve with the medication.


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