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COMMON NEUROLOGICAL CO-MORBIDITIES IN AUTISM SPECTRUM DISORDERS

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Abstract

Purpose of Review—Autism Spectrum Disorders (ASD) are heterogeneous neurodevelopmental disorders associated with various co-morbidities. Neurological co-morbidities include motor impairments, epilepsy and sleep dysfunction. These impairments are receiving more attention recently, perhaps because of their significant impact on the behavior and cognitive function of children with ASD. Here, we review the epidemiology, etiology and clinical approach to these neurological co-morbidities and highlight future research directions.

Recent Findings—Motor impairments include stereotypies, motor delays and deficits, such as dyspraxia, incoordination and gait problems. Sleep dysfunction typically presents as difficulty with sleep onset and prolonged awakenings during the night. Recent data suggest that abnormalities in melatonin may affect sleep and may be a potential treatment target. There is no classic epilepsy syndrome associated with ASD. Intellectual disability, syndromic autism and female gender are specific risk factors. Recent research has focused on identifying the overlapping pathways between these neurological co-morbidities and the core deficits in ASD, which may have direct and powerful implications for treatment and prognosis.

Summary—Motor impairment, epilepsy and sleep dysfunction are common neurological co-morbidities in ASD. Clinicians should be aware that recognition and treatment of these issues may improve the function and outcome of children with ASD.

Keywords

Autism; co-morbidities; epilepsy; movement disorders; sleep

INTRODUCTION

Autism Spectrum Disorders (ASD) are an increasingly recognized and extremely heterogeneous neurodevelopmental disorders defined by core impairments in social

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interaction, communication and restricted and repetitive behaviors [1]. Part of the heterogeneity is due to frequent and varied co-morbid conditions, such as intellectual disability, attentional problems, externalizing behaviors such as aggression, affective disorders, and sensory differences [2]. More recently, the neurological co-morbidities, namely motor impairment, epilepsy, and sleep dysfunction have been the center of active research. These neurological co-morbidities are not only common, but may have a greater effect on function and outcome than core symptoms alone [3]. Clinically, a comprehensive diagnostic assessment and management of children with ASD should include screening questions regarding neurological co-morbidities because specific intervention may improve overall function. This paper will review current knowledge on the epidemiology, etiology and management of these co-morbid neurological disorders and highlight implications for future research.

MOTOR DISTURBANCE

Motor dysfunction is prevalent in ASD yet only recently been the subject of research . Deficits have been documented in gait, coordination, and in the performance of skilled movements (praxis), with a recent study demonstrating that these deficits do not improve over early childhood [4*]. The characterization of motor impairments holds great clinical significance, as motor function is critical for broader aspects of development, including language, social interaction and learning (see Table 1). Furthermore, 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 creation of developmentally appropriate assessment tools and standardized scales to quantify and characterize motor impairment, particularly in infants and young children.

Repetitive behaviors

The only motor abnormality included in the diagnostic criteria for ASD is the presence of repetitive movements, also known as stereotypies. Recently there has been a growing appreciation for the fact that these likely represent an involuntary movement disorder rather than a “self-stimulatory” behavior. In a comprehensive study using video data on a large sample of children ages 2–11 with ASD, IQ matched children, and typical controls, investigators found that hand/finger and gait stereotypies were most specific to ASD, and that the prevalence of stereotypies was highest in the low functioning ASD group (70%) [5**]. Supporting the association of repetitive behaviors with more severe phenotype, one study found that repetitive movements were associated with lower IQ and more social and communication impairments [6]. Another study demonstrated that social skills intervention actually improves repetitive behaviors [7]. These studies suggest that stereotypies may predict clinical severity. Further investigation is needed to understand the cause of this association.

Motor delay

The identification of early motor delay holds particular clinical relevance, as early oral-motor skills and motor imitation have been shown to predict language acquisition in infants with ASD [8–11]. In a recent study comparing home videos of children with ASD,

developmental delay, and normal development in the first year of life, children with ASD demonstrated delayed development of motor skills including lying supine, sitting, and walking [12]. Several other studies have documented delays in motor development in the first two years of life, including postural abnormalities in unsupported gait [13*], less time spent in certain gross motor postures [14], and overall gross or fine motor delay [14]. One limitation to the use of retrospective home video is the lack of standardized direct assessments. However, the findings lay a promising foundation for prospective studies of infants at risk for ASD.

Gait

Gait abnormalities include toe-walking, ataxia, variable stride length and duration, incoordination, postural abnormalities in the head and trunk, reduced plantarflexion and increased dorsiflexion [15–19]. A very recent study by Nobile et al. used a novel automatic motion analyzer to characterize gait in children with ASD and typical controls. They found that children with ASD exhibited a stiffer gait with lack of “smoothness,” struggled to maintain a straight line, and showed evidence of poor postural control [20]. A strength of this investigation was the use of a quantitative, automated system to characterize a motor domain that can be challenging to objectively measure.

Incoordination

A meta-analysis of 41 studies investigating coordination, gait, arm movements and postural stability in ASD found that, despite the tremendous heterogeneity across studies, individuals with ASD exhibited significantly more motor incoordination and postural instability than controls. This difference occurred regardless of diagnostic category (i.e. autism vs. Asperger's), with an attenuation of effects with increasing age, suggesting improved motor function over time [21**]. More recently, in a population based twin-study, investigators identified a correlation between a standardized index of clumsiness and the subscale for autistic traits on the Child Behavior Checklist, suggesting a genetic etiological overlap regardless of clinical diagnosis. This study represents an important effort in using a motor domain to begin to define an endophenotype within the spectrum [22].

Performance of skilled movements (Praxis)

Using an examination of praxis in high-functioning children and adolescents with ASD, Mostofsky and colleagues have documented impairment in gestures to command, imitation, and tool-use, postulating that these deficits are rooted in impaired formation of spatial representation and poor motor execution. As with other motor domains, they have found that dyspraxia is significantly correlated to social, communication and behavioral deficits [23–25]. The same group found that dyspraxia also affected handwriting skill. In a separate study, the group showed that children with ASD showed poorer quality of letter formation compared to IQ matched controls. Moreover, handwriting quality correlated to overall motor skills in the younger cohort and to perceptual reasoning in the older cohort [23–27]. Another study also found a correlation with severity of phenotype, reporting that skilled movement impairments were most prominent in children with IQ < 70. While they conclude that the presence of dyspraxia may reflect overall neurological impairment [28], one could also posit

that deficits in early skilled movements affect learning, thereby contributing to cognitive impairment.

Future directions

Clearly motor deficits are prevalent in ASD, and certain types of deficits may be specific to the disorder. The pathophysiology and developmental course of the relationship between cognitive impairment and motor impairment must be investigated in more detail, as this relationship holds important clinical and prognostic implications. Treatments designed to target motor domains could theoretically improve cognition, social functioning and communication skills as well.

EPILEPSY

The increased risk of seizures in individuals with ASD has long been known [29]. In fact, recognition of this co-morbidity pointed to ASD as a neurological disease early on [30]. More recently, interest is growing in this overlap and the common pathophysiological mechanisms that may underlie both disorders. Table 2 provides a brief clinical summary of epilepsy among children with ASD.

Epidemiology

Most studies show that “syndromic” (non-idiopathic autism), intellectual deficits, and female gender all increase the risk of epilepsy in ASD. Several studies suggest that developmental regression is also a risk factor, but others show no association [31]. However, it is clear that, even in the absence of intellectual disability or co-morbid disorders, ASD is associated with an increased risk of epilepsy over the general population [32–34].

The rate of epilepsy in ASD is typically defined as 30%. However, critical review of the literature shows reported rates are highly variable, ranging from 6 to almost 50%. This is most likely a result of differing sample characteristics, such as ascertainment bias (e.g. population based samples vs. those drawn from a neurology clinical sample), as well as inclusion of individuals with more risk factors [31]. Conversely, rates of ASD in epilepsy populations are also increased, although exact numbers are not known and may be dependent on samples. Samples drawn from epilepsy clinics have reported rates of ASD in 15–30% [35, 36]; However, a recent prospective population based study showed only 5% had ASD [37]. Early onset seizures, especially Infantile Spasms, which are a severe early onset epilepsy often associated with poor neurodevelopmental outcomes [38] are associated with the development of ASD. Despite the variability in numbers, there is clearly an overlap between these two populations, which has important clinical implications since some studies show epilepsy increases mortality in ASD [39, 40].

Clinical Characteristics of ASD Patients With Epilepsy

Unfortunately for clinicians and researchers alike, there is no specific epilepsy syndrome in individuals with ASD. Age of seizure onset is bimodal, either in early childhood or adolescence [41*]. All seizure types have been reported, with recent studies showing that complex partial seizures (CPS) are the most frequent [36, 41*, 42]. This has particular

clinical significance, because the manifestation of CPS involves signs that are actually common behaviors in ASD (e.g. being unresponsive to name, repetitive movements, and eye deviation). This ambiguity makes the seizure diagnosis more challenging in this population.

The severity of the epilepsy is very variable. One recent retrospective review from an epilepsy center reported that 1/3 of patients had treatment refractory epilepsy. Early seizure onset was significantly associated with intractable seizures [43*]. Exactly how the presence of epilepsy affects the core features of ASD is still not well studied but lower social functioning and increased behavioral problems have been reported in a few studies [44, 45].

Occurrence of Epileptiform EEG Discharges

As with epilepsy, rates of reported epileptiform EEG are variable. Some investigators have suggested that frontal lobe discharges are more prominent [36, 42]. Some reports of high rates (up to 60%) of epileptiform EEG in the absence of clinical epilepsy [46, 47] have raised the question about a possible epileptic encephalopathy contributing to ASD pathophysiology. More research is needed on this topic

Evaluation and Treatment

Clinicians should have a high index of suspicion for seizures, and they should routinely inquire about behaviors consistent with seizures, especially in those with known risk factors. Given the heterogeneity of both epilepsy and autism, it is no surprise that there is no “one size fits all” diagnosis and treatment protocol. Current practice suggests that an EEG should be obtained in patients with a clinical suspicion of seizures [48]. Work-up should also include investigation for an underlying etiology. Some neurogenetic associations include Tuberous Sclerosis Complex [49], Rett syndrome [50], 15q11–13 duplication syndrome [51], and the recently described MECP2 duplication syndrome [52]. Metabolic disorders can also present with autism and epilepsy [53].

As with any epilepsy patient, anti-convulsant treatment choice is related to type of seizure, EEG findings, and tolerability of medication. Given the added complexity of the cognitive and behavioral deficit profiles seen in ASD, providers need to be particularly mindful of medication side effects [54**].

Future Directions - Understanding Pathophysiology

While clinicians strive to identify and adequately treat this important comorbidity, there is exciting research aimed at identifying possible pathophysiological mechanisms underlying the overlap of epilepsy and autism via investigations of specific signaling pathways in single gene disorders (e.g. tuberous sclerosis complex), genetic copy number variations [55], channelopathies [56], and gene network analysis [57]. This line of investigation will likely lead us closer to an understanding of the overlapping pathophysiology of epilepsy and autism with the express goal of developing more effective therapies.

SLEEP DISTURBANCES

Sleep problems are common in children with ASD and have significant effects on daytime functioning as well as quality of life of the children and their families. Table 3 provides a brief clinical summary of sleep disorders reported in the ASD population.

Rates and Risk Factors

Sleep problems are endemic in children with ASD, with a prevalence ranging from 40–86% [58–61]. The prevalence of sleep disorders among children with ASD is higher than children with other development delays [62, 63] and is unrelated to intellectual quotient (IQ) [64] or age [65].

Characterization of Sleep Problems

Data characterizing sleep in the ASD population have mostly been obtained through parental questionnaires, but objective methodologies have mostly confirmed these findings. Goldman et al. [65] reported results from 1859 validated parental questionnaires about sleep in children with ASD. The study found that younger children tended to have more reported sleep anxiety, bedtime resistance, more wakefulness during the night, and parasomnias; whereas adolescents reported more difficulty falling asleep, getting sufficient sleep and daytime sleepiness. Objective data from actigraphy, a watchlike microcomputer that measures motion, has shown that children with ASD take longer to fall asleep, have longer awakenings, and have more activity recorded at night compared to typically developing children [66]. One study using the gold standard of sleep characterization which is an overnight polysomnogram (PSG), showed that children with ASD have shorter sleep time and lower rapid eye movement (REM) sleep compared to children with typical development [67*]; however, these findings were not seen in prior research using PSGs [68, 69]. Based on the subjective and objective sleep measures reported, insomnia (e.g. difficulty falling asleep and staying asleep), may be the best way to characterize the sleep disorders reported in children with ASD [70].

Etiology

Insomnia may be a result of the core behavioral deficits of ASD as well as the co-morbid affective disorders commonly reported. Children with ASD may (1)ignore environmental cues that help entrain the sleep/wake circadian system; (2)perseverate on activities or thoughts that interfere with sleep onset or promote nocturnal wakings; (3) have communication limitations in understanding parents' expectations for bedtime [71]. Furthermore, children with more challenging daytime behaviors, such as hyperactivity or environmental hypersensitivities, may have more difficulties settling down to sleep. Co-morbid conditions such as epilepsy and psychiatric disorders, and their pharmacological treatments, may also affect sleep [72, 73].

More recent data have focused on the neurobiological mechanisms that may be involved in sleep disturbances among children with ASD. Melatonin is a neurohormone that is a robust biochemical signal of night and regulates the circadian rhythm. In a recent systematic review of the literature [74**], nine studies found at least one abnormality in melatonin production

among children with ASD. These abnormalities included below average physiological levels of melatonin and/or melatonin metabolites and abnormal melatonin coupling with the circadian rhythm.

Effects of Sleep Disturbances in Children with ASD

The relationship between sleep and behavior dysfunction in ASD is likely bi-directional. Sleep dysfunction has been associated with higher rates of autism severity scores, stereotypies, repetitive behaviors [75] and poorer social interaction skills [68]. In addition, recent research has shown that sleep is important in modulating affective brain processing and that sleep deprivation can contribute to emotional reactivity and difficulties in the interpretation of nonverbal social cues [76, 77]. Thus, sleep disturbance may contribute not only to the development of associated affective disorders but the expression of core communication deficits as well. A recent study also found that children with autistic regression had less efficient sleep, less total sleep time, prolonged sleep latency, prolonged REM latency and more wake time after sleep onset on PSG than children without regression [78*]. These findings, taken together, suggest that disturbed sleep and autism severity may be associated through common pathways such as disturbances in neurochemicals (perhaps melatonin, serotonin or GABA) and/ or neural circuitry.

Evaluation and Treatment

Given the high prevalence of sleep impairment in ASD, it is imperative for clinicians to include questions regarding sleep quality in the assessment and ongoing management of children with ASD. Sleep questionnaires such as the Children's Sleep Health Questionnaire [79] the Family Inventory of Sleep Habits [80] can help assess more detailed domains of sleep disturbances, sleep environment and family dynamics. Review of medications and assessment of psychiatric and neurodevelopmental comorbidities are also important in recognizing potential contributions to disturbed sleep. If sleep disordered breathing, parasomnias, nocturnal seizures, or periodic limb movements of sleep are suspected, referral to a sleep specialist and/or diagnostic evaluation with an overnight polysomnogram should be considered.

Currently, there are no Federal Drug Agency (FDA) approved medications for insomnia in children. A recent double blind, randomized, cross-over trial that evaluated 3 months of placebo vs. 3 months of melatonin use in children with ASD showed significant improvement in sleep latency and total sleep time with a low side effect profile [81*]. However, long-term use of melatonin has not been well studied.

Future Directions

While the high prevalence of sleep disorders and ASD is clear, objective characterization of the sleep disorders is limited. Neurochemical and neurophysiologic data are needed to fully characterize the reported sleep disorders in children with ASD, and they will contribute to our understanding of endophenotypes within the spectrum. Importantly, the impact of sleep impairments on cognitive function, affective regulation and emotional reactivity in children with ASD needs to be studied further given that treatment of sleep disorders will likely offer another target to maximize daily function and cognition in these children.

CONCLUSION

This review shows that neurological co-morbidities including motor abnormalities, epilepsy and epileptiform EEG abnormalities and sleep disturbance are relatively common in ASD. However, given the already heterogeneous and complex nature of this disorder they may go unrecognized in some circumstances. Because of their impact on day to day functioning of individuals with ASD it is crucial that clinicians screen for and adequately address these co-morbidities. Unfortunately, proper diagnostic evaluation, including formal motor testing, EEG and PSG/actigraphy, is often hard to obtain given behavioral difficulties and the sensory sensitivities so commonly seen in ASD, but that does not mean that these issues should not be addressed. We propose that referral for appropriate testing should be undertaken whenever indicated but a desensitization protocol may need to be considered. At this time there is not enough information to create a unifying hypothesis about the underpinnings of these deficits. But hopefully future research designed to further study the overlapping and underlying pathophysiology of motor dysfunction, epilepsy and sleep disturbance may even shine light on the causal mechanisms of the core deficits in ASD.

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Key Points

1. Neurological co-morbidities including motor dysfunction, sleep disruption, and epilepsy are common among children with ASD and can cause significant impairment to functioning and long term prognosis.
2. Motor dysfunction commonly reported in children with ASD include gross and fine motor delays, stereotypies as well difficulties with gait, coordination and praxis.
3. There is no specific epilepsy syndrome in individuals with ASD as the severity of epilepsy, location of EEG discharge and age on onset seem to vary.
4. The relationship between sleep and behavior dysfunction, mood and core impairments in ASD is likely bi-directional.

Table 1

Types of Motor Deficits in ASD

Type	Key Features
Stereotypies	Part of core features of ASD Associated with lower IQ and may be marker for overall ASD severity
Motor Delays	Could represent an early indicator for the development of ASD Early oral motor skills and motor imitation may predict language acquisition
Gait	Wide range of abnormalities including toe-walking, ataxia, stiffness, foot movement, and postural abnormalities
Incoordination	Seen in upper body movements, gait, and postural control
Dyspraxia	Found to significantly correlate with social, communication and behavioral deficits

Table 2

Epilepsy in ASD

Prevalence	Typically quoted at 30% but variable rates reported in the literature. Bimodal age of onset (young children and adolescents.
Risk Factors	Intellectual disability, syndromic ASD, female gender are associated with higher rates, but even those with high functioning ASD develop epilepsy at higher than population rates.
Evaluation	Careful clinical history but ASD behaviors make determination of seizure particularly difficult. EEGs are often helpful but often difficult to perform in these patients. Prolonged or overnight studies are more sensitive than routine.
Treatment issues	Clinicians must consider ease of administration and possible behavioral side effects when choosing anti-convulsant medications.
Other considerations	High rates of epileptiform EEGs have also been reported in children with ASD without clinical epilepsy, but clinical significance is unclear.

Table 3

Sleep Disturbance in ASD

Prevalence	Sleep problems are common in ASD (reported in 40–86%)
Features	Subjective and objective data indicate that children with ASD have difficulty falling asleep and sustaining sleep at night which may be best described as insomnia.
Evaluation	Parental questionnaires are available to assess sleep problems and bedtime habits. More objective data can be gathered from actigraphy and polysomnography.
Treatment issues	Behavioral and medication interventions are available but only supplemental melatonin has been well studied in this population.
Other considerations	Co-morbid diagnosis and medications need to be assessed for potential causes of sleep disruption.