Update in Development: Section B—Autism Spectrum Disorder

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Recently, a patient of mine who happens to be a very bright 10-year-old young man with an Autism Spectrum Disorder came into my office and sat down. Without asking me anything about my day, or what type of summer I was having he stated: "So Dr. Smith what can I teach you today? I know, tell me all the countries of the world in alphabetical order AND their capitals?" When I started to say that I could not do that, he quickly retorted: "Aren't doctors supposed to be bright?" And he quickly reeled off to me every country and its capital (IN ALPHABETICAL ORDER), some of which I had never heard of! He then proceeded to ask me if I knew the distance of Mars from Earth! This very bright young man has one friend at school, who is also on the Autism Spectrum. He is often seen walking around at recess reenacting video games or speaking Japanese to himself, which he learned from watching Yu-Gi-Oh on the internet!

Then there is an 8-year-old nonverbal boy with ASD who can spin anything in my office (including chairs), but struggles in school and is highly disruptive because of this fixation and his tendency to run out of the classroom.

Finally, there is a 16-year-old young lady, who first spoke at age 6-years, who can now tell me the **day** of my birth seconds after I tell her my birthdate, then she tells me "Man you are old!"

Such is the nature of some of my days in my Autism Clinic!

What Is an Autism Spectrum Disorder?

The autism spectrum disorders (ASD's) are a heterogeneous set of neurodevelopmental syndromes characterized by deficits in social communication and social interaction and the presence of restricted, repetitive behaviors. Social communication deficits include impairments in aspects of joint attention and social reciprocity, as well as challenges in the use of verbal and nonverbal communicative behaviors for social interaction. Restricted, repetitive behaviors, interests, or activities are manifested by stereotyped, repetitive speech, motor movement, or use of objects; inflexible adherence to routines; restricted interests; and hyper- and/or hypo-sensitivity to sensory input (American Speech-Language Hearing Association 2015). This results in the inability to engage in and benefit from many of the basic activities of life including but not restricted to conversing, learning, and engaging in meaningful and mutually beneficial relationships (Joseph et al. 2014).

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The purpose of this update is to provide a review of current literature pertaining to some of the more useful and practical innovations in the field, based on recent publications as well as some consensus. We have also taken the liberty of inserting some practical key points in the update. These are intended to facilitate acquisition of salient historical points, as well as demystifying presentation of the diagnosis to parents and caregivers.

We will begin by giving a general overview and then select a few important and possibly controversial topics to discuss. Throughout the chapter, we will attempt to make things easy to understand, practical and as much as possible, evidence-based.

Prevalence Update

Prevalence is the actual number of cases alive, with the disease either during a certain period of time (period prevalence) or at a particular date in time (point prevalence). Incidence is the rate of new (or newly diagnosed) cases of the disease. It is generally reported as the number of new cases occurring within a period of time (e.g., per month, per year, etc.). Thus incidence gives information about the RISK of acquiring a disease, while prevalence gives an indication of how widespread a disease actually is. The prevalence data for autism spectrum disorders appears to be a rapidly moving target. Current estimates range from 1 in 45 to 1 in 68 from the Centers for Diseases Control and Prevention-CDC (2014) (Zablotsky et al. 2015). Despite this, certain aspects of the demographic characteristics have remained stable over time. For example, the male-to-female ratio appears to be quite stable with a mean ratio of about 4 to 5:1, ranging from approximately 1.5:1 to 16:1 depending on the cognitive level being looked at. Boys are far more represented in the "higher functioning" group. However, both sexes are found throughout the intellectual spectrum. It is suspected that with the somewhat stricter criteria for diagnosis of autism spectrum disorders in the DSM 5, there may be a slight reduction in the frequency of diagnosis of some types of autism spectrum disorder, especially what used to be called pervasive developmental disorder, not otherwise specified (PDD-NOS) (Kullage et al. 2014; Smith et al. 2015).

Whether a true increase in autism spectrum disorders has resulted in the increase in ASD prevalence, or the latter is due to changes in community awareness, and identification patterns, is still not clear (Rice et al. 2012). However, these authors state that "disentangling the many potential reasons for ASD prevalence increases has been challenging. Understanding the relative contribution of multiple factors such as variation in study methods, changes in diagnostic and community identification, and potential changes in risk factors is an important priority for the ADDM network and for the CDC." Fombonne (2003a, 2005) states that "surveys conducted in the 1960s and 1970s only dealt with autism disorder (as opposed to ASD) and with a rather narrow definition of autism… and not accounting for autism occurring in subjects who are not "mentally retarded" (intellectually disabled). The closest estimate of ASD prevalence available in the late 1970s was 20 per 10,000 in a survey from the United Kingdom that was limited to the severely impaired children with ASD". He further stated that "rates of autism disorder in recent surveys have consistently been more than 10 per 10,000 whereas previous prevalence estimates ranged from 4 to 5 in 10,000" (Fombonne 2002). Therefore, he felt that from the available evidence it could be concluded that recent rates for both ASD and autistic disorder are 3–4 times higher than 30 years ago! Fombonne (2003b) concludes that the combination of the broadened definition (especially at the less severe end of the spectrum), possibly differences in methods for case finding, changes in referral patterns, availability of services, public and professional awareness, diagnostic concepts and practices, could all contribute to the apparent or real increase in prevalence.

As stated above, current data from the CDC, suggested that about **1 in 68** children have been identified with autism spectrum disorder (ASD) according to estimates from CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network. There was a sex differentiation with

approximately **1 in 42** boys being affected, and **1 in 189** girls living in the ADDM network communities being identified with an ASD. Worldwide, the prevalence seems to more closely approximate **1 in 100** (The Morbidity and Mortality Weekly Report 2014). The annual cost financially and otherwise to families and governments clearly is intimidating at the least!

What Causes Autism?

With the rapidly escalating prevalence of autism spectrum disorders, researchers worldwide are attempting to identify potential genetic and epigenetic factors that may play a role in causing this disorder.

Despite significant research documenting no link between the measles-mumps-rubella (MMR) vaccine and autism development, there persists a belief among parents that there is indeed a causal relationship, especially with regards to the regressive form. This has resulted in lower immunization rates in many countries.

Wakefield et al. (1998) in the Lancet, initially claimed an association between the autistic diagnosis and the presence of lymphoid hyperplasia and measles antibodies, in a since retracted publication which led to an unwarranted hype about the possible causal relationship between the measles vaccine and the development of regressive autism.

The recent publication in JAMA (Jain et al. 2015), where they looked at 95,727 children with older siblings, 994 (1.04%) were diagnosed with ASD, and 1929 (2.02%) had an older sibling with ASD. Of those with older siblings with ASD, 6.9% had ASD versus 0.9% who had unaffected siblings. These children were all privately insured in the United States of America. They concluded that there was no association between MMR vaccine receipt and ASD even among children already at higher risk for ASD! Taylor et al. (1999) in 1999 published similar findings in the Lancet, as did Madsen et al. (2002). Doja and Roberts (2006) did a literature review, and a Cochrane review (Demicheli et al. 2012) was published in 2012 on the subject, all of which found no support for any link. Anecdotally, and sadly, many of us have seen parents who opted not to immunize their second child after the first was diagnosed with the regressive form of ASD, only to have the second child subsequently be diagnosed. With increasing reports of outbreaks of measles in particular in various parts of the United States (CDC data; Centres for Disease Control and Prevention 2016), this raises new concerns about the health and well-being of these children. Measles can be a devastating disease causing serious pneumonias and other respiratory morbidities, but is also known to potentially cause a profound and progressive (but thankfully rare) neurological disorder called subacute sclerosing panencephalitis (SSPE). Accumulating data from various different sources, including genetic, neuropathological, electrophysiological, and even infant eye gaze preference studies, have suggested that the developmental pathways for autism are created much earlier than clinical symptoms are manifest—informing both the timing and the types of environmental exposures on which research should focus (Pierce et al. 2016).

Xiang and colleagues utilizing the large Kaiser-Permanente database, found that early onset (<26 weeks gestation) gestational diabetes increased the risk of ASD diagnosis (Xiang et al. 2015). Numerous studies have identified antenatal maternal stress as a possible "epigenetic" factor in autism spectrum disorders (Talge et al. 2007; Babenko et al. 2015; Grossi et al. 2016; Crawford 2015; Matelski L, Van de Water J 2016; Walder et al. 2014; Kinney et al. 2008). Severe maternal stress in pregnancy has been associated with lower cognitive and language abilities in childhood (Buss et al. 2010). King et al. (2012) reviewed the impact of natural disasters on neurodevelopmental disorders including autism using the Québec ice storm and Louisiana hurricane studies which revealed not only a "stress severity impact" but also a timing (gestation) impact. It appears that 5–6 months gestation is a particularly vulnerable period especially based on the Louisiana study (King et al. 2012). Beversdorf et al. (2005) suggested that pathological changes in the cerebellum in autism are thought to correspond to an event before 30–32 weeks gestation. In a retrospective study of 434 mothers of children with autism compared to 191 surveys to mothers

of children with Down syndrome, the researchers found a higher incidence of prenatal stressors in autism at 21–32 weeks gestation, with a peak at 25–28 weeks. Autoimmune disorders have also been associated with ASD (Sweeten et al. 2003; Molloy et al. 2006).

A relatively new (and somewhat controversial) area of interest involves the so-called "gut dysbiosis" phenomenon. GI symptoms are frequently reported in ASD and include constipation, diarrhea, food allergies/intolerance and abdominal pain. Rosenfeld (2015) reviewed the research re microbiome disturbances and autism spectrum disorders and the so-called "microbiome-gut-brain axis", and concluded that it was still premature to render definitive conclusions and establish causation but recommended further research. De Angelis et al. (2015) found altered fecal microbiota and metabolomes in children with autistic disorder and PDD-NOS compared to healthy controls. Mayer et al. (2015) suggest a possible benefit of probiotic treatment in rodent models of autism. Clearly further studies are required before this can be recommended in humans. In a review O'Mahony et al. (2015), they reviewed the evidence on the role gut microbes could play in childhood disease generation, including autism. They concluded that "it must be appreciated that there are complex relationships between host genetics, microbial interactions, and environmental factors that determine the risk of disease development. However, key developmental windows exist in the prenatal and postnatal periods that allow the microbiota to influence essential modulatory systems and vice versa". Potential areas for intervention or prevention were suggested. The higher prevalence of ASD in extremely premature infants adds further intrigue to the stress related hypothesis as well as the gut dysbiosis theories (Groer et al. 2015). It may be that for probiotics to have a role in prevention, they must be used EARLY in life, especially in high-risk infants (e.g., premature infants, and siblings of children with ASD, or perhaps even pregnant mothers). **Thus far, however, there is NO evidence of proven preventative or therapeutic benefit from probiotics use in other than possibly GI related issues.**

A Further Word About Risk-Factors

A number of factors have been identified as potential risk factors for ASD:

- Increased parental age (fathers ≥50 years; mothers 40–49 years AND <20 years; there was a joint effect of maternal and paternal age with increasing risk of ASD for couples with increasing differences in parental ages) (Lord and Bishop 2015).
- Both short and long inter-pregnancy intervals (IPIs) have recently been found to be associated with an increased risk of autism spectrum disorders (Sandin et al. 2016). Compared with children born to women with IPIs of ≥36 months, children born to women with IPIs of <12 months had a significantly increased risk of any ASD (pooled adjusted odds ratio [OR] 1.90, 95% confidence interval [CI] 1.16–3.09). This was less significant for long IPIs (Sandin et al. 2016).

Genetics

Autism spectrum disorder (ASD) is clearly a highly heritable condition (Agudelo et al. 2016). A number of authors (Packer 2016; Sandin et al. 2014) summarize by stating that a range of epidemiologic studies have supported the notion that ASD is multifactorial, with strong contributions from additive genetic and non-shared environmental risk factors. A very important recent finding was that de novo copy number variants (CNVs) are strongly associated with ASD risk (Sebat et al. 2007). To date at least 65 autism risk genes have been identified with several others showing strong potential (Packer 2016). It appears as if the future task of identifying the relationship between genotype and phenotype could be quite complex and challenging. Listing genes already identified as being significant is beyond the scope of this update. We strongly recommend the excellent review by Packer (2016) for this purpose. A recent study published in Nature Medicine (Yuen et al. 2015) and looking at quartet families with autism spectrum

disorder (two or more affected siblings with ASD) revealed that some 69.4% of the affected siblings carry different ASD-relevant mutations. These siblings with discordant mutations seemed to demonstrate more clinical variability than those who shared a risk variant. The authors concluded that there appears to be substantial genetic heterogeneity in ASD, necessitating the use of whole-genome sequencing (WGS) to delineate all the susceptibility variants in research and clinical diagnostics.

It is also very clear that a number of genetic syndromes have a higher than normal association with the development of autism spectrum disorder. These include DiGeorge syndrome (~20%), 22Q duplication, Angelman, Trisomy 21 (~8%), Fragile X (25–40%), 15q11–13 deletion, Tuberous Sclerosis (60%), Cornelia de Lange and others. Recent reports suggest an association between autism spectrum disorders and fetal alcohol spectrum disorders (Varadinova and Boyadjieva 2015; Evrard 2010). In clinical practice many of us working with this population certainly see features of ASD in many children with FASD.

ADHD and ASD share environmental and biological risk factors. Individuals with both disorders are more severely impaired than those with only one. There is strong evidence for genetic overlap between ADHD and ASD, demonstrating that rather than being an artifact of diagnosis, comorbidity is rooted in shared genetic risk factors (Antshel et al. 2013; Visser et al. 2016). A substantial minority of youth with ADHD demonstrate traits of autism spectrum disorder (15–25%), and interestingly, ADHD is one of the most common comorbidities in children with ASD (40–70%). Van der Meer et al. (2012) question whether autism spectrum disorder and ADHD represent different manifestations of one overarching disorder. A large number of copy number variants and chromosome abnormalities confer risks for ADHD and ASD (please refer to Van der Meer et al. (2012) for more details about this important and interesting phenomenon). In another great review by Craig et al. (2016) they reviewed the similarities and differences in executive dysfunction in these disorders. The ASD + ADHD group appeared to share impairment in both flexibility and planning with the ASD group, while it shared the response inhibition deficit with the ADHD group. Conversely, deficit in attention, working memory, preparatory processes, fluency, and concept formation did not appear to be distinctive in discriminating from ASD, ADHD, or ASD + ADHD group. Miodovnik et al. (2015), found that approximately 20% of children (who) had initially been diagnosed with ADHD before ASD were diagnosed with ASD ~3 years (95% confidence interval 2.3–3.5) after children in whom ADHD was diagnosed at the same time or after ASD. The children with ADHD diagnosed first were nearly 30 times more likely to receive their ASD diagnosis after age 6 (95% confidence interval 11.2–77.8). The delay in ASD diagnosis was consistent across childhood and independent of ASD severity.

The recurrence risk after one child is diagnosed with ASD approximates 20% (19–27%) (Schaefer 2016; Zwaigenbaum et al. 2012).

A "New" Finding

- Although the literature is quantitatively limited, some recent publications suggest a possible association between gender identity disorder (GID), or gender dysphoria (GD) and ASD. Skagerberg et al. (2015), looked for an association between GD and autistic features using the Social Responsiveness Scale (SRS). Approximately 46% fell within the normal range on the SRS, and of those 2.8% had an ASD diagnosis. 27.1% fell within the mild/moderate range and of those 15.6% had an ASD diagnosis and 6.7% and ASD query. Twenty-seven percentage also fell within the severe range and of those 24.4% at an ASD diagnosis and 26.7% in ASD query. VanderLaan et al. (2015) identified that high birth weight was associated with both high gender nonconformity and autistic traits among GD children. Pasterski et al. (2014) found less consistent data in adults with gender dysphoria. Schalkwyk et al. (2015) suggested that perhaps a more complex approach

that attempts to understand gender in developmental terms is potentially more salient for both research and clinical purposes. They also suggest that the current understanding about the unique social development of individuals with ASD, may impact the process of gender identity formation and thus underline the need for such an approach. In our clinic, we have recently had 4 patients self-identify as "transgender" or gender dysphoria.

Assessment/Evaluation

Autism spectrum disorder can be diagnosed reliably by age 2 by an experienced professional (Lord et al. 2006). For many children <3 years, early intervention can improve outcomes, including core deficits of ASD (social attention), e.g., language and symptoms severity (Dawson et al. 2010; Kasari et al. 2010).

Primary care providers have the opportunity to conduct developmental surveillance during well-child visits and monitor for early signs of delays including autism spectrum disorder at each visits.

Diagnosing a child with ASD takes two steps: (1) Developmental screening and (2) Comprehensive diagnostic evaluation. The American Academy of Pediatrics (AAP) recommends screening all children for ASD at 18–24 months of age. The modified toddler checklist for autism M-CHAT is a modified screening tool which can be used for children 16–30 months old during the well-child visits. This is a 23 item parent questionnaire with the structured follow-up interview to clarify items endorsed by parents. Recently Robins et al. (2014), validated a newer version of this instrument, the modified checklist for autism in toddlers, revised with follow-up M-CHAT-R/F. The questionnaire was reduced to 20 items with three risk ranges. Children in the low risk range (0–2) did not require follow-up interview unless <24 months of age, where a repeat screening after the second birthday is required. Children in the medium risk range (3–7) required the follow-up interview to clarify the risk of ASD, if at least two items remain positive, then preference for diagnostic evaluation was indicated. Children in the high risk range (8–20) were considered at sufficiently high risk to be referred directly for diagnostic assessment without the follow-up interview. The revised scoring increased the overall rate of ASD detection (67 versus 45 per 10,000 (Robins et al. 2014). The communication and symbolic behaviour scales infant toddler checklist CSBS-ITC, is a broad band screener to detect infants/toddlers (6–24 months) with communication delays including ASD from the general population. Positive and negative predictive value support the validity of the CSBS-ITC for children 9–24 months but not 6–9 months (Wetherby et al. 2008).

Historical Pearls

In trying to elicit a history consistent with an ASD diagnosis, it is sometimes difficult to be sure how to interpret the responses to our questions. Do parents REALLY understand what we are asking? Here are some ways to simplify this process:

- Does your child play ***WITH*** or ***AMONG*** other kids?
- Is your child a ***"creature of habit?"***
- Is your child a ***"stickler"*** for rules?
- Does your child like to ***"run"*** the show?

The above are questions that many parents of kids with ASD can relate to. I am amazed at the different reaction I get when I ask, "Does your child play with other kids?" vs. "Does your child play WITH or AMONG other kids?"

A similar question would include "HOW ***does*** your child play with other kids?"

[Sidebars are great for calling out important points from your text or adding additional info for quick reference, such as a schedule.

They are typically placed on the left, right, top or bottom of the page. But you can easily drag them to any position you prefer.

When you're ready to add your content, just click here and start typing.]

Children with positive ASD screens *and* clinician concern should be referred for further diagnostic assessment. Evaluation of ASD should include a comprehensive assessment by a team that has expertise in diagnosis and management. Since this is not always feasible, depending on the location or wait list, the diagnosis can be evaluated/confirmed by another pediatric specialist (psychologist, psychiatrist, neurologist, developmental pediatrician, general pediatrician) with expertise in ASD in collaboration with other team members (speech and language therapist, occupational therapist, teachers, etc).

Assessment includes a detailed neurodevelopmental history: current concerns, prenatal, perinatal, developmental history, medical, social and three generation family history (including mental-health history). Information and functioning in multiple settings e.g. home, school, after school programs and community by using rating scales, structured interviews and observations. For the parent interview, the ADI-R, though lengthy, has been established as a useful diagnostic tool in the assessment of ASD (Lord et al. 1994). Clinicians may decide to use other questionnaires if ADI-R is not feasible. The social communication questionnaire SCQ is the screening tool based on the ADI-R that can be used for children with a mental age over 2 years (Rutter and Barley 2003). Social Responsiveness Scale, second edition (SRS-2) is designed to identify social impairment that is seen in ASD and to differentiate it from social difficulties that occur in other disorders. It can be completed for children as young as 30 months to adulthood and takes about 15 min to complete (Constantino 2012). A useful tool for the evaluation of autism is the Autism Diagnostic Observation Schedule 2nd Edition (ADOS-2), which is a semi structured, standardized assessment of communication, social interaction, play and restricted and repetitive behaviours. Module 1–4 provide cut off scores for ASD and can be used in children as young as 31 months. The toddler module (12–30 months) of the ADOS provides ranges of concern reflecting the extent to which a child demonstrates behaviors associated with ASD (Lord and Rutter 2012).

Examination of the child should document growth parameters especially head circumference since children with ASD may have acceleration of head growth followed by stabilization (Courchesne et al. 2003). Look for dysmorphic features, neurocutaneous lesions and medical/genetic disorders that may co-exist with ASD e.g. Fragile X, tuberous sclerosis etc. (See also section "Genetic Disorders".)

Consider if the child has other co-existing or co-morbid conditions e.g. intellectual disability, language delays, developmental coordination disorder, ADHD, anxiety, etc., and carry out appropriate assessments for identification.

Investigations

All children with ASD should have an audiological exam and lead screening (if there is history of pica, or live in a high-risk area). EEG is not recommended routinely except when there is suspicion of subclinical seizures or clinical seizures and/or history of developmental regression. There is no evidence to support the role of clinical neuroimaging in the diagnostic evaluation of autism (Filipek et al. 2000). It should be performed based on clinical suspicion of existing alternative diagnosis e.g. Tuberous sclerosis, or presence of microcephaly or extreme (≥4 SD) macrocephaly, or focal seizures (Anagnostou et al. 2014). If a metabolic etiology is suspected magnetic resonance spectroscopy should be considered with standard neuroimaging. Metabolic testing should be guided by clinical indicators (seizures, neuro-regression, extrapyramidal signs, severe intellectual disability, failure to thrive, etc.). Suspicion of a particular genetic disorder helps in the selection of the specific genetic investigation since many recognizable syndromes have documented association with ASD (e.g. Fragile X, Angelman syndrome, etc.—see earlier) Chromosomal microarray (CMA) is a first-tier test in place of karyotype and the diagnostic yield is nearly 30% in complex ASD (congenital anomalies, microcephaly, seizures, dysmorphic features). Other

testing should include DNA testing for Fragile X in males, MECP2 sequencing in females with ASD can be considered with intellectual disability, MECP2 duplication testing in males if phenotype is suggestive, and PTEN testing if head circumference is >2.5 SD above the mean (Schaefer et al. 2013; Anagnostou et al. 2014). Where available, whole-exome sequencing may also be considered (Tammimies K et al. 2015).

Other testing should be dictated by the circumstances or history, for example, in a child with ASD who has highly selective dietary intake, nutritional screening for iron, zinc and vitamin B12 and others, could be considered (with the assistance of a dietician).

Treatment Options for Autism Spectrum Disorders

An excellent summary of treatments found to be effective in the management of ASD is provided by Anagnostou et al. (2014) in their review.

In their review they very succinctly summarize the treatment of autism spectrum disorders by stating: "The goal of existing interventions is to facilitate the acquisition of skills, remove barriers to learning and improve functional skills and quality of life."

Management is divided into **Behavioral** and **Biomedical** approaches.

Behavioral Interventions

Applied behavioral analysis (ABA) utilizing empirically derived basic learning principles, has been shown by many studies to produce meaningful and positive changes in behavior (Peters-Scheffer et al. 2011; Reichow et al. 2012) There are several models of ABA intervention all of which have some evidence to support their efficacy. There are still questions around timing, intensity and patient-selection for treatment to produce optimal effects, but in general it appears that early intervention is critical for this. A comprehensive review of this is provided in the paper by Zwaigenbaum et al. (2015). Several important statements, based on the review of a range of studies, and expert opinion were compiled. These included the following:

- "Current best practices for interventions for children aged 3 years with suspected or confirmed ASD should include a combination of developmental and behavioral approaches and begin as early as possible.
- Current best practices for children aged 3 years with suspected or confirmed ASD should have active involvement of families and/or caregivers as part of the intervention.
- Interventions should enhance developmental progress and improve functioning related to both the core and associated features of ASD, including social communication, emotional/behavioral regulation, and adaptive behaviors.
- Intervention services should consider the sociocultural beliefs of the family and family dynamics and supports, as well as economic capability, in terms of both the delivery and assessment of factors that moderate outcomes."

They also acknowledged the need to simultaneously address the comorbid conditions such as sleep disorders, gastrointestinal disorders (Bauman 2010), anxiety, and other maladaptive behaviors, in addition to seeking the assistance of occupational therapy and speech language pathology, when required.

Biomedical Interventions

Several studies have unsuccessfully attempted to identify pharmaceutical interventions which alter the core symptoms of ASD creating dysfunction. However, there are a number of studies now published which support the use of pharmacological agents to alleviate comorbidities affecting day-to-day functioning and quality of life of child and caregivers. These will be covered in more detail in the discussion of comorbidities later in this chapter. However, a few brief general points will be made here.

Perhaps the neuroleptics and stimulants have the most support for their use in the management of irritability/aggression. With the use of neuroleptics, the CAMESA guidelines should be carefully followed to monitor metabolic effects as well as potential hormonal impacts of their use (Pringsheim et al. 2011).

Comorbidities can significantly impact the quality of life of the child, caregivers at home and at school and therefore should be addressed, if it is possible to do this safely. The general premise is that it is often difficult to disentangle symptoms/comorbidities/ASD symptoms in every child. As a result, success in management is often not easily attained. For example, sleep disorders (see later discussion) are highly prevalent in the ASD population and can often result in irritable behavior, self-injurious behaviors, impaired focus, and hyperactive symptoms. In turn, sleep can be affected by anxiety, ADHD, medication use, etc. (Frye 2016). It is also important to recognize that children with ASD can also have medical problems, for example migraine headaches, which similarly can cause or exacerbate sensory and other issues. Sensory Integration Disorder (SID), now included in the DSM 5 as part of the ASD diagnosis also can significantly exacerbate other behaviors, and consultation with an occupational therapist competent with managing SID should be undertaken (McDonnell et al. 2015). Sensory disorders can affect a range of behaviors including feeding, sleep, attention, and can exacerbate as well as be exacerbated by anxiety. Management of GI issues, are beyond the scope of this update, but can be treated with the assistance of a gastroenterologist (Coury 2010). The Autism Treatment Network (Autism Speaks) also has excellent resources available for physician and parent use (The Autism treatment Network 2017).

Comorbidities in ASD

Comorbid conditions are common in ASD individuals though overlapping symptoms of ASD and other disorders often make diagnosis difficult.

Attention Deficit/Hyperactivity Disorder

ADHD occurs in 41–78% off children with ASD (Murray 2010). The DSM-IV did not allow the diagnosis of ASD and ADHD, however in the new DSM-5 this has been changed. It is important to consider the patient's ability to attend to both preferred and non-preferred activities since individuals with ASD may be able to focus for prolonged periods when engaged in preferred activities. ASD patients may be less responsive to methylphenidate than those with primary ADHD with a response rate of 50% and have a higher rate of side effects (e.g., irritability, self-injury, and stereotypy) (Mahajan et al. 2012; Reichow et al. 2013; Davis and Kollins 2012). Stimulants are recommended as first line choice in children with ASD and ADHD followed by atomoxetine and alpha agonists (guanfacine, clonidine) as second line and atypical antipsychotics as third line (Mahajan et al. 2012). Symptoms of ADHD can overshadow the symptoms of ASD, making diagnosis challenging. Children initially diagnosed with ADHD received their ASD diagnosis 3 years later then the children in whom ADHD was diagnosed at the same time or after ASD (Miodovnik et al. 2015). The coexistence of ADHD with ASD can significantly negatively impact the management and prognosis of ASD.

Irritability/Aggression (IA)

Approximately 20% of patients with ASD exhibit irritability/aggression at a moderate to severe range (Lecavalier 2006). Currently only two psychotropic medications, risperidone and aripiprazole, have been approved by the FDA for treatment of IA in individuals with ASD (Fung et al. 2016). Mood stabilizers such as Divalproex sodium (Hollander et al. 2010) and opioid antagonists (naltrexone) may decrease irritability in ASD but more clinical trials are required (Fung et al. 2016). Medication combined with behavioral intervention appears to be more effective for reducing aggressive behavior than medication alone (Dawson and Burner 2011). Novel treatments with glutamatergic

agents (amantadine, memantine, riluzole, NAC) are underway and encouraging results have been seen with N-acetylcysteine (NAC) when used as an adjunctive therapy to risperidone in deceasing irritability in children with ASD (Ji and Finding 2015).

Seizures

The prevalence of epilepsy in ASD varies from 5% to 38% and is related to underlying comorbid medical and intellectual disability. The risk of seizures and epilepsy increase with age. Every clinical seizure type has been noted in ASD. The prevalence of subclinical electrical discharges (SED) in ASD range from 30% to 61% in studies that have used long term EEG monitoring (Richard 2015). Studies have suggested that SED is common in childhood, while clinical seizures become increasingly prevalent with age (Parmeggiani and Barcia 2010). In individuals with ASD, the SED is multi-focal and includes temporal and frontal cortical areas and it has been suggested that SED may be associated with more severe speech and intellectual impairment in children with ASD (Richard 2015). Studies on individuals with SED but no ASD are associated with cognitive and behavior impairment which improve with antiepileptic medication (Pressler et al. 2005). Treatment of children with SED and ASD may be beneficial but further research is needed. Treating epilepsy in children with ASD follow the same principles as treatment of epilepsy in any individual.

Gastrointestinal (GI)

Gastrointestinal disorders are commonly associated with a subset of children with autism spectrum disorder. The prevalence of GI problems reported in children with autism spectrum disorder range from 9% to 91% depending on the definition used (Mannion and Leader 2014). The most common GI complaints in children with autism are constipation, diarrhea and gastroesophageal reflux and are treated in a standard manner. There is emerging evidence on GI dysfunction in ASD and the relationship of increased intestinal permeability, gut microbiome, immune function though scientific conclusions cannot be reached yet on interventions (Coury et al. 2012). Available data do not support the use of casein-free, a gluten-free diet or combination diets as a primary treatment for children with ASD, but results have largely been controversial as to whether there is any role, in the absence of diagnosed sensitivity or frank celiac disorder (Buie et al. 2010). In a largest study of its kind, researchers did not find any links between autism and celiac disease, though there was a strong association between autism and presence of antibodies to gluten suggesting gluten sensitivity (Ludvigsson et al. 2013).

Anxiety

At least one anxiety disorder is seen in 39.6% of the youth with ASD (Van Steensel et al. 2011). There is now evidence that anxiety may be "underdiagnosed" in this population, and standard anxiety screening tools may under-diagnose anxiety in these patients (White SW et al. 2009). The range of prevalence of anxiety disorders in the latter review was 11-84%.

Treatment recommendations include psychoeducational coordination of care and modified cognitive behavior therapy, which has been clearly shown to be beneficial especially in high functioning patients with ASD. It should be noted that anxiety can often present as inattention and restlessness, and therefore can mimic features of ADHD. It can also present as a sleep disorder, affecting both sleep initiation and night awakening. Patients with anxiety and ASD can also present with self-injurious behaviors and aggression. Specific phobias such as elevators, insects, thunder and lightning, etc. are not unusual. SSRI's are frequently prescribed for anxiety in youth with ASD though there is limited evidence unlike in typically developing youth with anxiety. Children with ASD may respond to far lower dosages than would be typically expected. As such, a liquid formulation is preferred, as this allows for lower titration (Folstein and Carcache 2016). SSRI's should be prescribed cautiously in youths with ASD with close monitoring (Folstein and Carcache 2016; Vasa et al. 2016). Some research also suggests the use of buspirone, or mirtazapine if SSRIs fail (Politte et al. 2015). It is also important to inquire about a family history of the mood

or anxiety disorder in these children, as there is some evidence that a high proportion of children with ASD and a mood/anxiety disorder also have a parent with a mood/anxiety disorder (Mazefsky et al. 2008).

Sleep Problems

Sleep problems are common in autism spectrum disorder, with prevalence rates of 40–80% (Cohen et al. 2014; Cortesi et al. 2010). Sleep issues include increased sleep latency, frequent night waking, and shorter sleep duration (Cortesi et al. 2010). It is worth noting that sleep onset and night-waking problems are often associated with poor sleep hygiene or maladaptive sleep associations. Good sleepers with ASD showed fewer affective problems and better social interaction then ASD poor sleepers (Cohen et al. 2014; Marlow et al. 2006; Cortesi et al. 2010). The reasons for sleep difficulties in children with ASD are multifactorial: poor sleep hygiene, medical issues (GI, seizures), medications, psychiatric issues (anxiety, depression, ADHD), abnormal melatonin regulation among others. Management requires addressing any medical or psychiatric issues that may interfere with sleep. Behavioural intervention (including sleep hygiene) can be effective in decreasing sleep problems and should be tried first, before medication (Cortesi et al. 2010). Addressing sensory issues may facilitate sleep in some children (e.g. weighted blankets). Light therapy can be considered for children with ASD who present with circadian dysfunction (Cortesi et al. 2010). Melatonin has been shown to be effective in a subgroup of children with ASD by decreasing the onset and improving the duration of sleep (Goldman et al. 2014). Low ferritin levels have been found to be associated with sleep disturbances in both children and adults, notably periodic leg movements and ADHD and studies have been done in the ASD population as well (Dosman et al. 2007).

Developmental Coordination Disorder (DCD)/Dyspraxia

Numerous studies have described motor impairments (Dyspraxia/DCD) in the ASD population (Dziuk et al. 2007). Children with DCD struggle with motor tasks like writing, dressing, self-care, and participating in sports, etc. This further negatively impacts social acceptance by peers. With the change to the DSM 5 a formal diagnosis of DCD can be made if the ASD individual meets the motor criteria, which is a change from the DSM IV-TR. Referral to a physiotherapist (PT) and occupational therapist (OT) is recommended in this scenario. Treatment modalities vary, depending on the areas of need (e.g. fine (FM) or gross motor skills, and presence of intellectual impairment). Generally, individual sports (e.g. swimming, or martial arts) are recommended for gross motor skills, and the OT will recommend FM adaptive devices, where applicable or computer software. For a great review of this topic please see Paquet et al. (2015).

Intellectual Disability (ID)

Intellectual Disability (IQ < 70) has been reported in 31% of children with ASD while 23% was in the borderline range (IQ 71–85) and 46% in the average or above range (IQ have increased >85) range. However, because of a variety of behavioral, language and mental health co-morbidities, getting an accurate assessment of intellectual functioning in children with ASD can be challenging. These individuals often "march to their own drum" and may not demonstrate their optimal abilities on queue. Children with IQ in the average to above range have increased in the last decade from 32% in 2002 to 46% in 2010. This shift in IQ may be attributed to a larger proportion of children with average to above average IQ being diagnosed with ASD (Buio 2014). As with all other co-morbidities, ID significantly impacts prognosis negatively. As noted earlier, all patients with ID warrant specific genetic, and possibly metabolic work-up.

Tics and Tourette Syndrome (TS)

Burd et al. (2009) studied 7288 participants from the Tourette Syndrome International Database Consortium Registry and found that 4.6% had a co-morbid autism spectrum disorder. Increased risk was noted in "male gender, no family history of tics/Tourette syndrome, and an increased number of comorbidities ($P < 0.001$)". Interesting

questions surface about the similarities between the two conditions, namely complex tics versus stereotypies, and OCD versus repetitive behaviors among others. Ordering and arranging compulsions occur in TS while lining up toys, etc., is commonly noted in ASD. Hoarding behaviors occur in both. Therefore, the notion is growing that, instead of viewing TS, OCD, ADHD, and autism as separate but co-morbid disorders, these disorders should be seen as part of a spectrum of disorders with overlapping etiologies, converging in dysfunctional cortico-striatal circuitry underlying these disorders (Huisman-van Dijk et al. 2016). Systematic review in another study revealed that the co-occurrence of ASD and TS is around 4–5% and the co-occurrence of ASD and tic disorder (TD) ranges from 9% to 12%. The comorbidity prevalence rates vary according to the level of ASD severity (with comorbidity of high-functioning ASD and TS reaching 20%) (Kalyva et al. 2016).

Summary

ASD is a fascinating and complex neurodevelopmental disorder. Future research hopefully will help sort out whether in fact ASD is a disorder in its own right or part of a broader spectrum of disorders possibly involving ASD, ADHD, DCD and Tourette Syndrome. The impact of comorbidities not only complicates and negatively impacts treatment but adversely affects prognosis.

The possible associations between maternal stress and ASD and other neurodevelopmental disorders is intriguing to say the least. Probiotics and the concept of the gut-brain connection with the microbiome also needs further research.

The true cause of the rapidly rising prevalence of ASD is still not fully understood, but there appears to be an increasing role for higher functioning individuals with ASD in our increasingly technological society (viz Silicon Valley). Are epigenetic factors causing an evolutionary drive to make future generations more capable of coping with our inevitably technological world?

Exciting times are ahead as we endeavour to look into these fascinating questions.

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