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REVIEW

A case of neurodivergence – the basics of autism spectrum disorder

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Introduction

Autism spectrum disorder (ASD) is a common neurodevelopmental disorder commencing in early childhood and is associated with neurological symptoms that are expressed as behavioural characteristics and vary depending on age as well as linguistic and cognitive abilities. To provide effective care and education, general practitioners should understand the needs of individuals with ASD and their caregivers.

Epidemiology

While prevalence estimates vary significantly between countries, it is estimated that 0.6% of individuals suffer from ASD, while as many as 9.9% of psychiatric in-patients meet the criteria for ASD.[1,2] Diagnosis of the disorder is more common in males than in females – while figures vary, the 2019 Global Burden of Disease Study reports a ratio of 3.23:1.[3] Although this may be attributed to increased susceptibility in males or even the effects of foetal endocrine disruption, it may also be due to underdiagnosis of ASD in females – possibly due to perceived and actual sex differences in language and social skills that blur symptom profiles between male and female patients.[4]

Various risk factors have been proposed to be involved in the pathophysiology of ASD. However, no concrete evidence exists to imply any one factor as causative. Importantly, neither vaccines nor the components thereof are associated with the development of ASD.[5] On the other hand, risk factors that are supported by evidence include trauma during birth, e.g. hypoxia, advanced parental age, maternal obesity, short inter-pregnancy interval, gestational diabetes, and maternal valproate treatment during pregnancy.[6,7] Intricate neurophysiological aberrations induced by these, and related factors may result from, among others, ischaemic/hypoxic damage, inflammation, and oxidative stress.[6]

Intersecting the above-mentioned risk factors, are a complement of heterogeneous genetic variants. These range from rare copy number variations (CNVs) that may have a profound impact on the individual's development to more commonly occurring single nucleotide polymorphisms (SNPs) that have a lesser albeit significant additive effect on ASD susceptibility.[8,9]

Pathophysiology

This interplay between an individual's genetic makeup and their environment contributes to neurodevelopmental disorders during windows of vulnerability in foetal and neonatal development – a time during which the CNS is especially susceptible to external insults due to the complex biological events that govern brain development.[10]

While the underlying mechanism of ASD is by no means clear or well understood, it is believed that its pathophysiology mainly revolves around aberrant brain plasticity and synaptic structure. Ultimately, this leads to imbalanced coordination of neuronal inhibition and may result in abnormalities in various neuronal circuits.[11] In parallel, evidence indicates brain overgrowth – especially during the first two years of life.[12] However, conflicting evidence and opinions exist that such overgrowth may then either persist or normalise during the later stages of childhood and even be followed by degeneration during late adulthood.[11–13]

Importantly, the pathophysiological profile of ASD has been found to extend beyond the brain. Many individuals diagnosed with ASD – up to 9 out of 10 – also experience gastrointestinal abnormalities that include increased intestinal permeability, dysregulated motility and secretion, and dysbiosis of the gut microbiome. This is compelling, considering the increasingly recognised role of the gut-brain axis in neurodevelopment and brain health. Accordingly, increased gut permeability and altered functioning of the enterochromaffin cells may lead to peripheral hyperserotonaemia and immune dysregulation also commonly observed in ASD.[11,14]

Symptoms, screening, and diagnostic criteria

The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) established a single category of ASD, replacing previously included subtypes of autistic disorder, e.g. Asperger syndrome, and unspecified pervasive developmental disorder.[15] The symptoms of ASD – atypical neurodevelopment in functional areas that manifest as behavioural characteristics – are clustered into two domains (see Table I).

In essence, individuals diagnosed with ASD have difficulties in communicating and understanding others, resulting in limited eye contact and impaired use of non-verbal gestures,

including facial expressions. In children, these characteristics may be accompanied by abnormal social communication and interaction along with restricted or repetitive behaviours or interests.[16,17] As such, early symptoms that may alert health professionals or caregivers to the risk for ASD include an inability of the child to respond to their own name and an absence of interest in pretend play and interactive games. Restrictive or repetitive behaviour, on the other hand, may be expressed as obsessive interests, getting upset by changes in toys, colour or order or even repeating words or phrases (echolalia).[17,18]

The Autism Diagnostic Observation Schedule, second edition (ADOS-2) serves as the gold standard for trained providers to assess individuals of varying age and linguistic ability suspected of having ASD. In South Africa, the tool has been translated and adapted to assess children from different cultural and socio-economic backgrounds.[19,20] The results supplement general developmental screening of language, cognitive and motor delays to aid DSM-based diagnosis of ASD. Assessment should ideally be a multidisciplinary process that involves the caregivers and includes routine full paediatric physical examinations.[17]

Importantly, to fulfil the diagnostic criteria for ASD, all three symptoms of social affective difference need to be present, accompanied by at least two of the four symptoms related to restrictive and repetitive behaviours. ASD may occur with or without medical, genetic, neurodevelopmental, mental, or behavioural disorders, or an intellectual or language impairment and be stratified along three levels of severity according to the degree of support required by the individual.[15]

Table I: Diagnostic criteria for ASD (adapted from DSM-V-TR)[15]

Domains		Criteria
A	Persistent deficits in social communication and social interaction *(all sub-criteria need to be present)*	Deficits in: • social and emotional reciprocity • nonverbal communicative behaviours • developing, maintaining, and understanding relationships
B	Restricted, repetitive behaviour, interests, and activities *(at least two sub-criteria need to be present)*	• Stereotyped or repetitive speech and behaviours • Insistence on sameness/ resistance to change • Restricted, fixated interests • Hyper- or hyposensitivity to sensory input
C	Signs or symptoms must be present during early development, but they may not be fully evident until later, when social demands exceed limited capacities, or they may be masked by learned strategies.	
D	Symptoms interfere with everyday functioning.	
E	Symptoms are not better explained by intellectual disability or global developmental delay.	

Some children with ASD who display average or above-average intelligence may not be identified until entry into the school system or even later in life, when social demands increasingly challenge their ability to adapt, impacting their function.[21] Considering that the DSM-5 criteria have been demonstrated to adequately identify younger children and those with mild symptoms, it is crucial that such children be diagnosed early, considering their potential to respond to timely intervention.[21,22]

A variety of comorbid conditions commonly co-occur in children with ASD, contribute to phenotypes observed in ASD and may affect symptom presentation. These include behavioural diagnoses, e.g. attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder, as well as mood and anxiety disorders and sleep disorders. The methodology and findings of epidemiological studies on the prevalence of intellectual disability in ASD vary. While earlier reports indicated that the vast majority (upwards of 70%) of ASD patients suffered from intellectual disability, more recent reports indicate much lower, but still significant, figures around 30%.[16,17,23] Furthermore, there exists a positive relationship between intellectual disability and epilepsy in individuals with ASD – approximately a quarter of ASD patients develop epilepsy and the risk for epilepsy increases as IQ decreases.[24] Clearly, the symptoms of several behavioural, neurodevelopmental, and other disorders may overlap with ASD or even co-occur, highlighting the importance of a proper differential diagnosis (see Table II).

Table II: Differential diagnosis in children with ASD (adapted from[16,17])

Differential diagnosis	Children without ASD typically…
Severe hearing impairment	make eye contact and reciprocate sign-based interaction.
Intellectual disability	reciprocate social interaction; demonstrate linguistic development consistent with their intellectual ability.
Developmental language disorders	do not display restricted, repetitive behaviour or deficits in social communication.
Selective mutism	lack pervasive symptoms exhibited by children with ASD.
Obsessive-compulsive disorder	dislike rituals associated with their diagnosis; display normal social behaviour and linguistic development.
Reactive attachment disorder in response to severe neglect	apply the language skills they have, albeit deficient; display gradual normalisation in behaviour communication when moved to a normal social environment.
Childhood psychosis	display normal language comprehension; develop normally up to diagnosis.
Landau-Kleffner syndrome	lose established language skills; proceed to develop EEG abnormalities.

Management

Considering that no cure exists for ASD, the primary treatment goal is to minimise deficits in social communication and interaction as well as impairments in behaviour that may interfere with the development of functional skills. By doing so, the individual has the best chance to achieve functional independence and develop skills that may assist them in compensating for the above-mentioned deficits. Caregivers, therefore, need to be assisted in getting access to structured educational and behavioural interventions and developmental therapies that are appropriate for the age, ability level and potential comorbidities of the child with ASD.

Considering the heterogeneity of ASD, the use of pharmacotherapy – should it be required – needs to be individualised based on symptoms exhibited by the patient and aim to optimise the efficacy of psychological and educational interventions. The use of risperidone and aripiprazole has been demonstrated to be effective in managing behavioural difficulties, including irritability and aggression in children with ASD.[16,17,25] To control ADHD, either non-stimulant or stimulant approaches may offer value. Stimulants, e.g. methylphenidate, are more appropriate and deliver better results in higher-functioning ASD patients. However, in individuals with OCD and/or repetitive and restrictive behaviour, stimulants may potentiate such symptoms and a non-stimulant approach, e.g. atomoxetine, clonidine, and tricyclic antidepressants, may therefore be more appropriate.[16,17,25] Although selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed in ASD, limited evidence exists for their efficacy in treating repetitive or restrictive behaviours in the disorder while their use has been associated with adverse outcomes in children.[25,26] Lastly, considering the previously mentioned propensity for epilepsy in ASD, anticonvulsants are also commonly prescribed. However, little evidence exists for the use of anticonvulsants, e.g. valproate and carbamazepine, as mood stabilisers in ASD.[17]

Summary

Delayed and aberrant social, communication and cognitive skills arise during early childhood in individuals with ASD. Due to the syndromal expression of this neurodevelopmental disorder, it poses challenges for the child, their caregivers, and clinicians alike. To best manage this, multidisciplinary care is essential and should involve a coordinated approach from general practitioners, paediatricians, psychiatrists, clinical psychologists, educational specialists, occupational therapists, and others. When treatment modalities, either psychological, educational, or pharmacological, are employed it is essential that empirical data supports the use thereof in ASD.

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