Of Rain Men and Snowcakes: The presentation, pathology, aetiology and management of autistic spectrum disorder

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Over the past two decades, both the prevalence and our understanding of autism have increased exponentially. Autism encompasses a group of behaviourally defined developmental disorders, collectively known as autism spectrum disorder (ASD), which appear to be caused by the impact of environment during early life on genetically induced susceptibility. As paediatricians are consulted first by most parents of children with developmental delay, they should be able to discuss the pathology, aetiology and management of the disorder. Although much remains to be understood, research over the last 20 years has shown that this disorder is treatable, and that early medical/biomedical and behavioural intervention greatly improves the quality of life and outcomes of children with ASD.

Over the past 20 years, research into the causes of autism has expanded due to technological advances in basic and medical science. The portrayal of autistic individuals by the entertainment media in films such as 'Rain Man' and, most recently 'Snowcake', as well as the publicity surrounding the suggested role of vaccines in the causation of the disorder, has heightened public awareness of this condition. Because parents are most likely to approach a paediatrician when concerned about their child's development, it is imperative that paediatricians be able to recognise warning signs of autism and explain the pathology and causation of this condition, and be familiar with local management and intervention options available.

Epidemiology

Autism is a complex developmental brain disorder defined by a core triad of symptoms, namely impaired communication and social interaction as well as restricted and repetitive interests and activities.[1] The prevalence of autism in the USA and Europe has increased dramatically from 2 - 5 to 15 - 60 per 10 000 children; whether this is due to the use of broader diagnostic criteria, greater awareness, and/or a real rise in the number of cases due to altered environmental factors is not currently clear.[2,3] In South Africa no statistics on autism are available, but there is no reason to think that the prevalence of the condition, which knows no socio-economic or ethnic boundary, will be any lower. Typically boys are more frequently affected than girls, with a male/female ratio varying from 2:1 to 15:1 depending, among other factors, on the particular form of autism.[4]

Clinical signs and symptoms

The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), characterises different pervasive developmental disorder categories: Autistic Disorder (AD), Asperger's Syndrome (AS) and Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS). However, the presence and intensity of DSM-IV symptoms are highly variable between individuals, perhaps pointing to further aetiologically defined subtypes; the term autistic spectrum disorders (ASD) is therefore currently favoured to describe these conditions collectively.[5] Furthermore, ASD often coexists with other genetic, psychological and biological conditions that need to be considered in the differential diagnosis and management of a child presenting with ASD symptoms (reviewed in Naber *et al*.[6]).

Parents of ASD children might recognise their child as being somehow 'different' during the first few months, or, more typically, seek advice during or soon after the child's second year of life because of a perceptible language delay and lack of compensatory non-verbal communication efforts. Alternatively, some apparently normally developing children may suddenly regress and lose developmental and language skills, usually between the ages of 2 and 4 years.

Although presentation of ASD is extremely varied, social deficits, including the lack of joint attention (defined as manifest enjoyment of sharing an object or event with another person by looking back and forth between the two) appears to be a reliable and early warning sign of ASD in infants.[6] These 'good babies' are often content to be alone, and do not appear to seek eye contact or attention via gestures or vocalisation.

At a later age, some AD and PDD-NOS children may have some speech, which often involves repeating script from favourite TV programmes or repetition of another person's speech (echolalia). Some children also develop 'giant-words', where phrases are condensed into single utterances, e.g. 'whereareyou?', while being unable to combine words into new phrases that convey true meaning.[4] AS children, on the other hand, are often quite verbose about restricted topics of consuming interest to them, but are unable to express feelings or recognise the viewpoints or interests of others.

Older ASD children may also demonstrate atypical behaviours such as stereotypies including repetitive hand or finger movements, strange eye gazing, sniffing, licking, persistent toe-walking, rocking and twirling. These 'self-stimulatory behaviours' may have sensory underpinnings and, although often harmless, are problematic because they may hamper learning and appropriate play. Severely affected ASD children, particularly those with severe intellectual disabilities, may also demonstrate self-injurious behaviours, which are often triggered by change, frustration or fatigue.[7]

Although it was once considered that up to 70% of ASD children are cognitively impaired, recent studies assessing fluid intelligence, rather than the Wechsler scales of intelligence, suggest that intelligence has been underestimated in ASD individuals.[8]

Although ASD predominantly involves dysfunction in the central nervous system (CNS), individuals with ASD demonstrate multiorgan system involvement, even in the absence of co-morbid syndromes.[9] As such, many children with ASD present with inattention and hyperactivity, atypical motor development, disturbed sleep patterns, immune dysregulation and inflammatory conditions.[10-13] The vast majority show sensory processing difficulties, often involving all sensory modalities, and ranging from hypo- to hypersensitivity even within the same modality (for example auditory hypersensitivity to environmental noise, but under-responsiveness to a human voice).[14] Additionally, more than two-thirds of ASD children manifest gastrointestinal (GI) symptoms, including abdominal pain and distension, gastro-oesophageal reflux, inflammation of the GI tract, chronic constipation or diarrhoea, and dysbiosis.[15,16] Between 35% and 46% of ASD individuals also develop epilepsy, with onset usually around puberty.[17]

Prognosis is dependent on many factors, including the severity of symptoms and presence of comorbid conditions, capacity for joint attention, cognitive abilities and functional play skills; better outcomes are associated with early intervention programmes and inclusion into regular educational settings with typically developing peers. Although, with intervention, many ASD children may function fairly well in mainstream schools, some will manifest attention-deficit hyperactivity disorder (ADHD) or other learning challenges, while outcomes in adulthood appear to correlate best with cognitive-adaptive abilities.[4]

Pathology

Children with ASD demonstrate increased head growth, even when indexed to body length, during the first year or two of life compared with neurotypically developing children.[18,19] This initial increase in brain growth has been associated with an overgrowth of white matter, or myelinated fibres, which is thought to result in aberrant neural network development, with elaborate short-distance cortical connections *within* brain regions and hemispheres but reduced large-scale, long-distance connections *between* regions.[9] Additionally, further pathological changes have been noticed in the corpus callosum, amygdala and cerebellum of ASD brains.[20,21]

Aetiology: genetic, immune and environmental factors

ASD is highly heritable, with monozygotic twins showing between 60% and 92% concordance and a sibling recurrence rate of 3 - 8%, indicating a strong genetic component in the causation.[22] Correlations exist between regions of chromosomes 2, 7, 1 and 17 and ASD, and genes implicated to date include some involved in neurodevelopment, neuronal growth, synaptic and dendritic changes and neurotransmission.[23] Some of the proteins implicated by these genetic studies have pleiotropic functions, and may account for the multisystem involvement seen in ASD. Candidate gene studies also imply that differences in neurochemical levels (e.g. melatonin, serotonin, dopamine, glutamate, GABA and endorphins)[24,25] as well as metabolism (impaired sulfoxidation and carbohydrate metabolism)[26,27] between ASD and neurotypical individuals may have genetic underpinnings.

None of the described genetic alterations are ubiquitous across all ASD cases, and it is accepted that, in ASD *per se*, genetic changes by themselves are unlikely to be sufficient to cause the disorder. Rather, ASD is probably precipitated by the action of the environment during early life, including fetal life, on a substrate rendered susceptible by genetic factors.[1]

During the first and second trimesters of pregnancy, environmental factors such as teratogens, maternal illness, particularly viral infections, and maternal and paternal age, as well as fetal testosterone levels, are thought to increase ASD risk to the child.[4]

The immune system is also implicated by the presence of autoantibodies against brain proteins in almost 40% of ASD subjects, as well as by studies showing increased complement proteins in the peripheral blood and gastrointestinal tract of ASD individuals.[28] Moreover, the cytokine profiles in ASD individuals are often skewed towards T-helper cell type 2, while lymphocyte numbers and T-cell mitogen response may be decreased.

Despite earlier claims that thimerosal, a mercury compound, in childhood vaccines contribute to the causation of ASD, removal of most thimerosal from vaccines has not led to reduction in ASD incidence in California.[29] However, as mercury is a known neurotoxin, the role of environmental mercury exposure is still unclear.[30] Similarly, reports concerning the association between MMR vaccination and onset of ASD are conflicting.[31]

Moreover, approximately 40% of ASD children demonstrate intestinal permeability, so that digestion products of natural foods are able to induce antigenic responses.[32] It has been proposed that the partial breakdown products of gluten and casein, which have been shown to cross the blood-brain barrier and elicit opioid effects in rats, and which are present in the urine of some ASD children, may be responsible for autistic behaviours in some children.[33] Removal of gluten and casein from the diet has been reported to reduce ASD symptoms; however, further controlled studies with larger sample sizes are required in order to reach unambiguous conclusions about this approach.[34]

Management

Early diagnosis

Early identification of ASD is crucial as it allows early intervention at physical, behavioural and medical/biomedical level, which has been demonstrated to improve aberrant behaviour and cognitive impairment.[2,35] Although checklists and diagnostic criteria are available for identification of autism, their interpretation in terms of measurable behaviours is often difficult for those not experienced in recognising this disorder, particularly in very young children. In addition, checklists of symptom patterns are often broad enough to be indicative of many differential diagnoses, rather than specifically indicating early signs of ASD, and children with higher intellectual functioning are often missed. In Table I we therefore summarise key warning signs of ASD, drawn from the DSM-IV, Childhood Autism Rating Scale (CARS) and Checklist for Autism in Toddlers (CHAT), and attempt to give paediatricians concrete ways of eliciting these in very young children, so that they can be alerted to the need for further investigation by professionals such as developmental and educational psychologists as well as occupational therapists to confirm a diagnosis of ASD. These signs refer predominantly to social indicators, as these are often the symptoms that differentiate ASD from other disorders, and should be used together with a background of DSM-IV diagnostic criteria. Because siblings are at significantly increased risk, young non-autistic siblings should also be monitored closely for early warning signs.[36]

Medical/biomedical

An integrative medical approach is needed to manage ASD, and treatment should be individualised in view of the variable presentation. Pyschopharmacology is effective in reducing symptoms of behavioural problems but further studies are required, as evidence is limited, with some exceptions, to uncontrolled studies that do not include all age groups.[37] Currently, the only medically registered treatment for certain ASD symptoms is risperidone, a well-known antipsychotic used in the symptomatic management of irritability, agitation, aggressive and self-injurious behaviour and temper tantrums.[38] Co-morbid obsessive-compulsive disorder, general anxiety disorder, or major depressive disorder are treated with selective serotonin-reuptake inhibitors, while methylphenidate, clonidine and atamoxetine are used as supporting medication where attention deficit symptoms, hyperactivity and impulsivity are present.[39] Anticonvulsant therapy may be indicated where epilepsy and seizures occur, while melatonin may be of benefit in the treatment of sleep disorder.[40]

Furthermore, it should be remembered that these children are metabolically fragile and often benefit from biomedical intervention, including dietary intervention, nutritional support and supplementation.[41,42] A change in behaviour, such as temper outbursts or self-injury, may be caused by occult gastrointestinal discomfort.[7] Concomitant metabolic or immune disorders need to be diagnosed effectively. Parents may also require guidance about the use of alternative interventions, such as herbal remedies and homeopathic treatment.[42,43]

TABLE I. CHECKLIST FOR EARLY WARNING SIGNS OF AUTISTIC SPECTRUM DISORDER IN YOUNG CHILDREN

Question	Test
Does the child respond consistently to his name being called?	Call **just** the name, without giving an instruction, while the child is engaged in an activity. Do this twice during the consultation to determine consistency. Response refers to the child looking towards the person calling. *Note*: calling must be by a stranger, and not a parent, to ensure that response is to his/her name and not to recognition of a familiar voice.
Does the child show shared attention and read gestures?	Point to something across the room, and observe whether the child follows the gesture, e.g. point to a toy while saying 'Look at that [toy] on the bookshelf.' Ask the child to point to something **other** than an object they may find desirable, e.g. 'Show me your nose', or 'Where's the light?' The child should be able to do **both**.
Does the child show expectation/anticipation during brief pauses in play?	Play a peek-a-boo type game with the child (for example, hide your face and reappear unexpectedly and then **repeat** this action). The child should show facial signs of anticipation.
Does the child reference the parent's face for reassurance?	Pick the child up unexpectedly during the consultation and observe the child's reaction. The child should look at the parent for help/reassurance.
Does the child exhibit basic imitation skills?	Say: 'Do this' and then perform a basic action such as clapping your hands or putting your hands on your head. The child should **copy** your actions immediately.
Can the child answer social questions?	Ask the child social questions such as 'What is your name?' or 'How old are you?' The response should **not** be reliant on verbal ability, but can include a show of fingers or a partial verbal response.

If the child is unable to give a positive response to at least five of these questions, further investigation by a professional trained to diagnose ASD, such as a psychologist or psychiatrist, is necessary. Averted gaze, absence of a social smile, resistance to social engagement, sensory problems (which may be indicated by fussy eating, sensitivity to noise, arching of the body and difficulties in potty training), and language delays are further indications of increased risk of ASD. Parents may be directed to Autism South Africa (http://www.autismsouthafrica.org) or the authors for information about further intervention resources.

Behavioural

Numerous studies have shown the benefits of initiating intervention programmes in children with ASD as early as possible, including increased IQ and social skills, and reduced aberrant behaviour.[35,44] Behaviour intervention programmes can be home- or centre-based, but are most effective when skills learnt at centre-based programmes are reinforced daily in the home environment.[45] Effective interventions include applied behaviour analysis (ABA, used to increase and maintain desirable adaptive behaviours, reduce repetitive behaviours and generalise new skills to novel environments), discrete trial teaching (applied within an ABA framework to improve attention, compliance and discrimination learning), TEACCH (involving the used of a highly organised physical environment, and predictable sequences of structured activities to improve skills) and relationship development intervention (activities that elicit interactive behaviours so that the child may discover the value of and become motivated to sustain positive social interactions).[7] Additionally, therapies aimed at remediating processing capacities, such as occupational therapy, including sensory integration, and speech and language therapy are requisite to the rehabilitation of ASD children.[7,46] Some South African early intervention programmes are listed on the Autism South Africa website (http://www.autismsouthafrica.org).

Families

Management should also be extended to care of the family of an ASD child, as anxiety and depression are higher in parents of children with ASD than those with other developmental syndromes.[47] Support should include emotional support, guidance and help in locating useful intervention resources and referral for counselling or other appropriate services. Most importantly, parents need to be educated about ASD and the efficacy of early interventions in treating and rehabilitating their children.

Conclusions

While ASD has in the past been called the most devastating of childhood developmental disorders, progress in ASD research has brought a clear message in recent years: while autism remains challenging to manage and requires a multidisciplinary approach, it is treatable, and early medical/biomedical and behavioural intervention significantly improves the quality of life of both these children and their families.

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