Table of Contents

Executive Summary............................................................................................................................4
Introduction.......................................................................................................................................4
Autistic regression and optimal outcomes.......................................................................................6
Autism as a whole-body disorder: Current state of knowledge.........................................................6
Increased morbidity and mortality in autism and the lack of medical care....................................8
Neuroinflammation and immune dysregulation in ASD.................................................................9
Autoimmunity in ASD......................................................................................................................10
Autistic regression and its association with infection, autoimmunity and inflammation...............11
Allergic diseases in ASD..................................................................................................................12
Immunity and inflammation in ASD: Improving long-term outcomes by translating research into clinical practice........................................................................................................13
Gastrointestinal comorbidities and abnormal bacterial flora in ASD.............................................13
Non-coeliac gluten sensitivity and ASD..........................................................................................15
Metabolic abnormalities, acquired mitochondrial dysfunction and oxidative stress in ASD.........17
Seizure disorders in ASD..................................................................................................................19
Motor dysfunction, connective tissue disturbance and movement disorders in ASD..................20
Sensory dysfunction and abnormal pain reactivity in ASD............................................................21
Dysfunction of the autonomic nervous system and HPA axis in ASD..........................................21
Conclusion.......................................................................................................................................23
Approaching comorbidity in the ASD patient: Medical considerations.........................................24
References.........................................................................................................................................26
Related publications by Thinking Autism.......................................................................................38
Preventing Diagnostic Overshadowing and Identifying Medical Comorbidities in ASD: A summary guide sheet for healthcare professionals......................................................39
Executive Summary

Autism spectrum disorder (ASD) is a complex and highly heterogeneous neurodevelopmental condition. While ASD is diagnosed based on the presence of persistent challenges in social communication, and restricted/repetitive behaviours, many common medical conditions are also now recognised to be significantly more prevalent in people with ASD compared with the general population. Premature mortality is also significantly increased in ASD. Yet, according to widespread reports and published case studies, symptoms of medical conditions, sometimes severe, are often overlooked and simply attributed without investigation to ‘behaviours’, ‘mental health issues’ or just ASD itself.

Difficulties with communication can represent a significant barrier to the reporting and diagnosis of any potential health condition and prevent individuals with ASD from accessing appropriate health care. A person with ASD often communicates through behaviour. A change in behaviour can be related to an underlying health problem. Difficulties recognising health issues can be compounded if a parent or a carer is not aware that certain symptoms (i.e. behaviours) should be reported as important, especially if these symptoms have been previously dismissed as being part of ASD. The onus is on healthcare and other professionals working in partnership with parents and carers to recognise and respond to these challenges in order to adequately diagnose and treat people with ASD.

The fast-changing research literature is summarised in this document in order to support all responsible parties towards understanding the possible mechanisms of symptomatology, behaviours and other possible consequences of comorbidity and underlying medical conditions in ASD, thus enabling improved patient care, enhanced quality of life for people with ASD, reduced dependency and decreased long-term costs.

Introduction

The prevalence of ASD is currently estimated between 1-2% (Baio et al., 2018; Zablotsky et al., 2015) with a strong upward trend of diagnoses (Mannen et al., 2020; Russell et al., 2015; Waugh, 2019; Xu et al., 2018a). The ongoing rise in prevalence is not confined to any geographic areas, but is instead reported by countries throughout the world (Kim et al., 2011; Sun et al., 2019). Various explanations have been put forward for the increase including a widening of the diagnostic criteria, case ascertainment, diagnostic substitution and increased awareness of the heterogeneity of ASD (Hertz-Picciotto and Delwiche 2009; Rice et al., 2012).

“Adults with ASD have a significant burden of major psychiatric and medical conditions. Their underlying impairments in social communication and related sensory symptomatology likely impede the delivery of preventive health care. Improved strategies for delivering the most appropriate and effective health care are needed for this growing population.” (Cren et al., 2014)

A true increase in the number of people being diagnosed with autism (or being labelled as autistic) (Russell et al., 2015). Several lines of evidence support this assertion. Grether and colleagues (2009) in their analysis of the California Department of Developmental Services (DDS) data (a dataset that tracks individuals with autism who require significant support needs in California) concluded that diagnostic substitution from mental retardation (i.e. genotype/phenotype) to autism was “unlikely to explain the increase in DDS clients with autism.” This is set against a backdrop of an unremitting rise in ASD cases reported by the DDS, from 3902 persons in 1987 to 108,100 in 2018. At a country-wide level, other datasets also show increasing numbers of people being diagnosed with autism seemingly unaffected by changes to diagnostic practices. Data from the Department of Health in Northern Ireland, tracking changes to the numbers of children with autism in Northern Irish schools (Waugh, 2019) have shown a year-on-year increase in numbers. For example, in 2009 around 21% of school-aged boys were diagnosed with ASD. In 2019, this had increased to 5%, with many more children still awaiting formal assessment. This and other data contribute to the idea that autism is increasing and such an increase is not wholly driven by changes to diagnostic practices.

“The most challenging component of management lies in assessing and interpreting the presenting symptomatology, and considering medical conditions among the possible underlying causes.” (Smith et al., 2012)

ASD is a highly heterogeneous disorder; the aetiologies are both varied across individuals and complex. There is a general consensus that ASD results from a diathesis between genetic and environmental factors (Lyall et al., 2017). Genetics is what each individual is born with; what is inherited from our parents. The environment is what influences our development, from preconception, to any potential influences occurring during pregnancy, at birth and postnatally. What we ingest (i.e. eat, breathe, or absorb through our skin) and our experiences represent the environment. An estimated 40-55% of the variance in risk of ASD is attributed to environmental factors (Halmayer et al., 2011; Sandin et al., 2017). Even in identical twins, where both twins are diagnosed with ASD, there is variation in the severity of the autism symptoms that can be attributed to environmental factors (Castelbau et al., 2020). One study that looked at the rate and severity of autism in identical twins found that the siblings with a history of early medical problems have much higher rates of autism compared to their genetically identical siblings who did not experience such adverse events. This provides further evidence for external environmental factors influencing genetic make up. Those non-shared adverse environmental events and factors include problems in pregnancy and during delivery (e.g. foetal distress, hypoxia, infections (e.g. ear infections), allergy and epilepsy (Willfors et al., 2017).

Several environmental factors so far have been found to be associated with the risk of ASD. These include prenatal infections, the presence of immune and autoimmune issues in mothers, foetal exposure to toxins, pollutants and certain types of medications, pregnancy complications, maternal stress, health and nutrition, and advanced paternal age (Emperti Gialloreti et al., 2019; Gebun et al., 2017; Miller et al., 2017; Modabbernia et al., 2017; Sun et al., 2020).

There are various monogenetic disorders that carry a high risk of ASD, such as Rett Syndrome, Fragile X or Down Syndrome, illustrating how varied aetiologies and pathways result in a similar set of behavioural symptoms (Gilberg & Coleman, 2000). Outside of known genetic disorders, most susceptibility genes that have been found to increase the risk of ASD are linked to mechanisms of host defence and adaptation to environmental factors—in other words, environmental risk factors potentially contribute to ASD only under specific environmental circumstances (Nazeen et al., 2016; Saffari et al., 2019; Saxena et al., 2012; Tamouza et al., 2020).

Additionally, children with various congenital disorders, where a physical abnormality or disease is present from birth, are more likely to develop ASD compared to healthy controls. The disorders with high rates of autism include cerebral palsy (Craig et al., 2019; Pålhaman et al., 2020), congenital heart defects (Bean Jaworski et al., 2017), muscular dystrophies (Colombo et al., 2017), tuberous sclerosis complex (Mitchell et al., 2017; Wilbur et al., 2017) and neurofibromatosis Type 1 (Morris et al., 2016).

CASE EXAMPLE 1

Munair is a 5-year-old boy with regressive autism. He was progressing reasonably well when he developed what looked like self-harming behaviour. Munair would frequently strike his jaw forcefully, jump from his bed, and refuse to eat. He was underweight and undernourished despite good intake. Amoxicillin was prescribed to help with his recurrent ear infections, but Munair was still jumping, scratching and pulling his ears. Munair was underweight and undernourished despite good intake. Amoxicillin was unsuccessful. Azithromycin helped significantly, but discontinuation led to recurrence. A five-day course of azithromycin followed by every other day dosing led to a sustained and substantial improvement. The jaw-striking and jumping was thought to be an attempt to unblock his ears.

"Comorbidity is to be expected in autism spectrum disorders — directly or indirectly. Comorbid conditions may be markers for underlying pathophysiology and request a more varied treatment approach."

**Autistic regression and optimal outcomes**

Accumulating scientific evidence challenges the previously-held belief that all autism is an inborn and unchangeable condition. Numerous studies now confirm that typically developing children can lose some of their developmental milestones in areas of social communication and behaviour, including previously acquired language and social skills, and regress into autism. Regressive autism is seen in around 30% of all autism cases. There also seems to be a connection between regression and poor long-term functional outcomes (Gain-Kochel et al., 2014; Tan et al., 2021).

The reasons and mechanisms behind autistic regressions are largely unknown, in part because children who experience a regression, at the time when autism is typically recognised, are rarely the subject of detailed clinical investigations (see section ‘Autistic regression and its association with infection, autoimmunity and inflammation’ for discussion on known reasons behind autistic regression).

Frequently noted around the time of regression is the onset of symptoms of physical distress such as fever, irritability, vomiting, incessant crying, sudden changes in sleep patterns, as well as novel dietary restrictions, sensory dysfunction and in some cases, the emergence of movement disorders. Autistic regression and physical changes can occur suddenly within days or be progressive and evolve gradually over a period of several months. While in most cases autistic regression occurs between the ages of 12–24 months, several studies have reported unusual onset patterns, including regressions involving severe and/or sudden-onset motor dysfunction, recurring regressions and/or regressions after age three years (Scott et al., 2017; Thompson et al., 2018).

On the other hand, an optimal developmental progression has been observed for some children on the autism spectrum presenting with decreasing symptoms, or even complete recovery from ASD (Eriksson et al., 2013; Mukaddes et al., 2014; Oestreicher et al., 2014; Ozonoff; 2013; Whiteley & Byrnes, 2018). The study by Deborah Fein and colleagues in particular challenges the assumption that ASD is static and lifelong. It provides strong evidence that recovering from autism is indeed possible and opens up the possibility of improvement, even without optimal normalization.” (Fein et al., 2019).

Further studies are required to identify the exact reasons why some children develop the symptoms of autism following a period of normal development, or experience considerable worsening of symptoms and severity of ASD, whilst others diagnosed with ASD sometimes progress to such a great extent that they lose their diagnosis (Ickinci et al., 2012; Eriksson et al., 2012; Thurm et al., 2018). It is, however, now well established that specific biomedical abnormalities such as neuroinflammation and immune dysfunction, GI problems, abnormal stress response and metabolic dysfunction are associated with the severity of the condition. Each of those biomedical comorbidities can have negative impacts on behaviour and neurological functioning. Successfully addressing such issues can lead to significant improvement in overall functioning and wellbeing for individual people.

**Autism as a whole-body disorder: Current state of knowledge**

Studies published in the peer-reviewed domain over the last decade confirm many earlier findings of widespread biomedical abnormalities as being present in cases of autism. While ASD has been commonly referred to as a neurodevelopmental and behavioural disorder solely affecting brain functions and kept within the disciplinary boundaries of psychiatry and neurology, it is now increasingly being recognised as a whole-body disorder or condition. Integrating knowledge across different areas of medicine and science—immunology, gastroenterology, and endocrinology, for example—has progressed our understanding of autism. The combination of scientific and medical research, what is referred to as biomedical, provides an in-depth means of analysis and understanding of autism.

“Several lines of research lend hope to the idea that biomedical treatments may someday improve the prognosis for a larger majority of children diagnosed with ASD.” (Helt et al., 2008)

**CASE EXAMPLE 2**

Edward is a 14-year-old boy with a history of severe regressive autism. He presented with an 18-month history of altered behaviour. Sub-acute onset of self-harm, agitation, frequent night waking and latterly, aggression against others. Appetite was variable but largely maintained. stools were reported as normal against a background of long-standing constipation. GP had referred to paediatrician, who referred to a paediatric gastroenterologist, who referred on to a neurologist. He was commenced on carbamazepine for mood-stabilisation. At consult he was agitated, preferred to sit, but frequently stood straight, pacing. He required constant one to one supervision, provided by his father. Edward struck his father twice during the consultation. He had no speech. No further examination was possible. He was re-referred to gastroenterology, referred on to a general surgeon and underwent a semi-urgent gastric fundoplication. Aggressive behaviour has not recurred.

**CASE EXAMPLE 3**

Max is a 13 year old by with high functioning autism. He presented with a 2-3 year history of increasingly labile mood, obstinance and some mild cognitive impairment. Behaviour and performance had begun to affect his school placement. Examination revealed grossly pitted and erythematous tonsils. Bloods revealed an ASOT of 800 (nr > 200), mildly elevated platelets of 420 (nr > 400) and marginally elevated ESR of 11 (nr > 10). Results remained abnormal over time with only partial response to antibiotics. Max was referred to EHT, and subsequently underwent a tonsillectomy. Within two weeks mood improved, obstinance ceased and his school grades returned to normal.
Increased morbidity and mortality in autism and the lack of medical care

Early mortality is significantly increased in ASD, with death rates being three to ten times higher than the general population (Bilder et al., 2013; Hwang et al., 2019; Smith et al., 2019; Woolfenden et al., 2012). These deaths tend to be the result of complicating medical conditions, such as epilepsy, as well as gastrointestinal and respiratory disorders (Gillberg et al., 2010; Pickett et al., 2011; Shaftelle et al., 2001) alongside accidental causes of death resulting from risky and dangerous behaviour.

A 2014 survey conducted by Thinking Autism of families with ASD (n=340) only 22% of respondents reported that “the person with ASD had a thorough investigation of his/her symptoms from a [National Health Service] practitioner”. When asked what type of symptoms NHS professionals had dismissed as the result of ASD, answers included frequent diarrhoea, screaming, self-injury, sleeping only a few hours a night, severe-like behaviours, aggressive outbursts, failure to grow, comforting/posturing, excessive drinking of water, toe-walking, chewing/ eating non-food items, tics and jerks. Only 10% of respondents were “very satisfied” with their experience of NHS GPs (General Practitioners) and paediatricians, while 51% and 46% respectively were “unsatisfied”; 80% of respondents had sought private medical help for their children with ASD (Thinking Autism survey, 2014).

Impairments in communication and social interaction are by definition core symptoms of ASD and play a role in the challenges clinicians face in diagnosing medical comorbidities. However, current knowledge indicates that many of the symptoms and behaviours that frequently occur in autism have been erroneously assumed to be a result of autism itself, vaguely labelled as a mental health/psychiatric problem. Some of those symptoms and behaviours include aggression, agitation, irritability, impulsivity, lack of focus, disturbed sleep, self-harming, self-stimulatory behaviours, a lack of coordination, and visual, tactile, and auditory oversensitivity.

These challenging behaviours have a substantial negative impact not only on the individual with ASD, but also on families and society as a whole (Cheely et al., 2012; Geluk et al., 2011; Gossage et al., 2007). One investigation found that 68% of children with ASD had demonstrated aggression to a caregiver and 49% to non-carers (Kanne and Mazurek, 2011). The costs, both human (Hodggets et al., 2013) and monetary (Buescher et al., 2014; Cidav et al., 2012; Lavelle et al., 2014), reflected by these statistics are incalculable.

In addition to reports by carers, published case studies provide examples of diagnostic overshadowing and illustrate how easily behavioural manifestations can be overlooked due to lack of awareness on the part of healthcare providers (Goldson and Bauman, 2007; Jones et al., 2008; Lea et al., 2012; Smith et al., 2012). It could be argued that dismissal of the atypical manifestation of pain and physical issues as merely ‘autism behaviours’ represents outright discrimination towards people, wherein a person is treated less favourably than someone else and that the treatment is for a reason relating to the person’s protected characteristic”, that is, their disability (Equality Act 2010).

The American Academy of Pediatrics in their widely distributed Autism A.L.A.R.M. document (2004), encourages clinicians to listen to parents, because they “generally DO give accurate and quality information”. However, it is also important to recognise that there may be communication challenges between parents or carers and their child with autism and that this problem is exacerbated if the caregivers are unaware of the possible implications of the symptomatology, especially if at any point they have been told that behaviours are ‘simply autism’. Thus, we argue that healthcare providers must ensure that parents and carers understand that behaviours in autism can be physical in origin, identifiable using thorough and appropriate investigations, and typically manageable or treatable with appropriate health care.

Neuroinflammation and immune dysregulation in ASD

A large proportion of individuals with ASD show signs of persistent neuroinflammation, altered inflammatory responses, and immune abnormalities. The severity of these immune disturbances has been found to correlate with the severity of ASD symptoms. Furthermore, these immune disturbances are thought to play a central part in the pathogenesis of the disorder. Both population-wide studies and experimental animal research point to immune-related pathways being directly involved in the development of ASD symptoms and manifestations (Carlezon et al., 2019; D’Staso et al., 2019; Masi et al., 2017; Thom et al., 2019; Young et al., 2016).

“Immune dysfunction plays a major role in the pathophysiology of ASD.” (Abdallah et al., 2014)

Some of the key ASD susceptibility genes identified through genome wide analysis (GWA) studies are involved in inflammatory signalling, immune function and infections, further strengthening the link between immune dysfunction and ASD (Bennabi et al., 2018; Gupta et al., 2014; Tamouza et al., 2020). Other studies have also revealed a genetic association between ASD and autoimmune disease, such as multiple sclerosis (Jung et al., 2011). Mothers of children later diagnosed with ASD have been found to present with abnormal levels of pro-inflammatory markers indicative of immune dysfunction (Brown et al., 2014). Additional epidemiological studies have revealed a link between prenatatal infection and/or immune activation, maternal and infantile immune disorders, atopic diseases and family history of autoimmunity and risk of ASD.

CASE EXAMPLE 1

Steven is a 5-year old boy with marked regressive autism. He suffered sleep disturbance, self-selected dietary restriction and marked hyperactivity. He could follow no commands. He ate only dry, starchy food. Parents had placed a plastic shield over their TV due to Steven continually slapping the screen. On examination he had marked tonsillar enlargement with marked erythema, and reactive anterior cervical lymphadenopathy. Blood showed mildly raised inflammatory markers and elevated eosinophils. He was commenced on a protracted course of co-amoxiclav for strep throat. Within three weeks he had calmed, seemed happier and widened his diet. He began obeying one and two stage commands. Parents reduced potential allergens in the bedroom and he began sleeping through the night.

CASE EXAMPLE 2

Joseph is a pleasant 10-year old boy with regressive autism. Visual learning was markedly improving, but speech and listening skills were disproportionately behind. He had a long history of ear infections with grommet insertion twice before. Further ENT review revealed failed grommets, reinsertion with titanium grommets failed too. He did not respond to allergy management, a trial of antihistamines and a protracted course of azithromycin. He was duly referred to an immunologist, and subsequently found to have a mannose-binding protein deficiency. He has made good progress on long-term prophylactic antibiotics.
higher in families of individuals with ASD compared to the general population. These conditions include asthma, psoriasis, coeliac disease, type 1 diabetes, rheumatoid arthritis, autoimmune thyroid disease, and antiphospholipid syndrome (Chen et al., 2016).

“Antibrain antibodies do play an important pathophysiologic role in autism. Prenatal and/or postnatal exposure to these antibodies enhances autism severity by impairing cognitive processes and adaptive functioning, boosting motor stereotypes, altering the sleep/wake cycle, delaying or halting neurodevelopment especially in reference to verbal and non-verbal language. Our adverse pathological consequences of auto-antibodies in independent samples, support the potential use of anti-brain antibodies as biomarkers predicting autism severity and clinical features of ASD, while possibly providing new avenues for preventive and therapeutic strategies.” (Piras et al., 2014)

Higher levels of various brain-reactive auto-antibodies can also be detected in some mothers of children with ASD compared to mothers of typically developing children. The presence and levels of such autoantibodies have been linked to both the presentation and the severity of core autistic symptoms (Bauman et al., 2014; Frye et al., 2013a; Piras et al., 2014; Ramirez-Celis et al., 2021). The adverse pathological consequences of auto-antibodies are demonstrated in primate animal research studies. In such studies, the antibodies isolated from the mothers of children with autism are found to correlate with an alteration of typical brain development and to result in social behaviour abnormalities in offspring (Bauman et al., 2014; Gata-Garcia and Diamond, 2019). It is estimated that maternal auto-antibody-related (MAR) autism could account for one in ten cases of autism (Brinimbeg et al., 2013). Children with ASD and a family history of autoimmunity also may have high levels and increased frequency of systemic serum antinuclear autoantibodies, capable of causing tissue damage via multiple mechanisms, including neurotoxicity (Mostafa et al., 2014).

Research reports have recommended further study into the possible correlation between an ASD and/or PANDAS (Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections) or PANS (Paediatric Acute-onset Neuropsychiatric Syndrome) and ASD (Goncalves et al., 2018). PANDAS/PANS are autoimmune conditions which disrupt typical neurological function. The conditions are often clinically acute; infections or vaccinations include manifest as rapid or relatively rapid onset obsessive compulsive disorder (OCD) and/or motor tics (Orlovskia et al., 2017), alongside other behaviours that potentially fit the diagnosis of ASD.

“Autistic children who are seropositive to systemic antibodies with high titres should be followed up clinically at regular intervals of time to detect the possible development of symptoms and signs of systemic autoimmune diseases” (Mostafa et al., 2014)

Autistic regression and its association with infection, autoimmunity and inflammation

While the mechanisms behind most cases of autistic regressions are largely unknown, in rare instances there are defined circumstances—identified by detailed clinical investigations—around the reasons for regression. These cases include the onset of an autoimmune reaction, typically manifesting as anti-NMDA-Ab encephalitis and the recovery from autistic symptoms and neurological impairments following appropriate treatment (Armangue et al., 2013; Creten et al., 2011; Gonzalez-Toro et al., 2013; Hacohen et al., 2016; Scott et al., 2014) Caused by an autoimmune reaction to neuronal NMDA receptors, NMDAR-Ab encephalitis is a well-characterised clinical-immunological syndrome. Symptoms in children are loss of language and social skills and reduced interest in surroundings, hallmarks of an ASD diagnosis. Other presenting features in children can include seizures and/or status epilepticus, sleep disturbances, temper tantrums, lack of appetite, dystonia, abnormal gait, tics, hyperactivity, psychotic episodes, irritability, agitation and aggression (Matoq et al., 2015; Schimek et al., 2008), each of which, in varying degrees of severity, can commonly present in idiopathic autism.

Healthcare professionals must be aware of the potentially important role for autoantibodies in some cases of ASD, particularly in those individuals who have a familial history of autoimmune-related diseases and/or seizure disorder.

Other cases of well-documented autistic regression involve encephalopathic illnesses of viral origin. While acute illnesses caused by a herpes virus, especially cytomegalovirus, are the most frequently reported ones (DeLong et al., 1981; Ghazuddin et al., 2002; Gilberg, 1986; Iverson et al., 1990; Kajima et al., 2012; Libbey et al., 2005; Sakamoto et al., 2015; Stubbs, 1980; Sweeten et al., 2014), there are also documented case reports of enterovirus encephalitis leading to autistic regression, including loss of previously acquired language and developmental milestones in a previously healthy toddler (Marques et al., 2014), as well as reports of autistic regressions, including late-onset ones, following malaria and pneumococcal meningoencephalitis (Badaqara et al., 2011; Mankoshi et al., 2006). Another example of this phenomenon is paediatric HIV-encephalitis, where presenting autistic symptoms and behaviours are indistinguishable from idiopathic autism and can in many cases be reversed or alleviated with antiretroviral therapy (Brouwers et al., 2004; Moss et al., 1994; Tepper et al., 1998; Wolters et al., 1994).

Preliminary reports of prolonged steroid therapy improving long term outcomes in children with regressive idiopathic autism lend weight to theories that inflammatory and/or immune-related processes

**CASE EXAMPLE**

Jameel is a 5-year old boy. He developed normally until 15 months of age when he experienced 3 weeks of continuous fever. His communication, socialisation and behaviour became affected from that point; he lost all speech and eye contact, and presented with marked sleep disturbance, and self-restricted diet. Gastrointestinal symptoms were present early on including a sharp deterioration in speech, cognition, executive functioning and motor coordination, and increased anxiety and irritability (Adams et al., 1984; Mynt et al., 2009; Niranen et al., 1988). Equally, animal model studies have shown that proinflammatory agents can precipitate the emergence of ASD-related symptoms (Dada et al., 2014; Filiano et al., 2016; Foley et al., 2016; Mantler et al., 2008; Rose et al., 2017). Instilling of animals who are exposed to immune stressors during pregnancy such as infections or allergies can develop deficits in social interactions and communication, repetitive/stereotyped behaviours, sleep disturbances and epileptiform activity that closely mimic diagnostic symptoms and common comorbidities of ASD (Nold et al., 2017; Missig et al., 2018; Patterson, 2019).

**Autoimmune In ASD**

Autoimmune disorders are conditions in which the immune system wrongly perceives the "self" tissue of the body as being "non-self." He has therefore launched an immune response against healthy cells, tissue, or organs, resulting in a disease or dysfunction in a part of the body. The prevalence of autoimmune conditions is significantly higher in families of individuals with ASD compared to the general population. These conditions include asthma, psoriasis, coeliac disease, type 1 diabetes, rheumatoid arthritis, autoimmune thyroid disease, and antiphospholipid syndrome (Chen et al., 2016).
play a causative role in autistic regression (Duffy et al., 2014). Unfortunately for patients and their families, in most cases the circumstances of autistic regression do not normally trigger medical inquiry.

**Allergic diseases in ASD**

In recent years there has been an increased recognition of behavioural and neurological symptoms such as anxiety and mood disorders being possible manifestations of allergic disease, appearing alongside classic biological markers and physical manifestations (Chang et al., 2013; Khandaker et al., 2014). Allergic reactions can potentially cause or worsen hyperactivity, irritability, difficulties in focusing, daytime fatigue and sleep disturbances in both young people and adults (Dahl et al., 1995; Shyu et al., 2012). Effectively addressing allergy and allergic reactions can sometimes have a positive impact on behaviour, and reduce anxiety and mood disorders (Goodvin et al., 2012).

“But in our study, with the largest case number reported thus far, the results supported the significant association between ASDs and allergic diseases.” (Chen et al., 2013)

Children and adults with ASD suffer significantly higher rates of allergic disease (Lu et al., 2020) compared to the general population. Various allergic manifestations, including asthma, nasal allergies, atopic diseases (IgE-mediated) and food intolerances appear to be correlated to the severity of core autism symptoms (Chen et al., 2013a; Croen et al., 2015; Kohane et al., 2014; Lyall et al., 2015; Schieve et al., 2012). Moreover, the presence of allergic disorders in ASD is also correlated to problem behaviours such as anxiety, hyperactivity, and irritability, commonly attributed to ‘being autistic’ or to having ‘mental health’ problems (Mostafa et al., 2008; Shibata et al., 2013).

It has been demonstrated that a challenge with nasal allergens results in an increase in autism symptoms in a total of 16 children studied (Boris and Goldbait, 2004) while treatment of allergies often results in improvement in negative and challenging behaviours and better overall functioning (Chen et al., 2013b; Jyonouchi, 2010; Schieve et al., 2012). While it is commonly assumed that discomfort and pain associated with allergic diseases simply aggravate behavioural symptoms, there is reason to suspect, as discussed above, that the association of autism with allergic disease is due to shared pathological mechanisms (Angelidou et al., 2011; Kordulevska et al., 2019; Mostafa and Al-ayadhi, 2013; Yadama et al., 2020). Additional evidence that allergic neuroimmune activation may underlie core autism-related behavioral abnormalities in some cases has been provided by experimental animal studies (de Theije et al., 2013; Schwartz et al., 2015; Tonell et al., 2009).

“Allergic conditions are easily treatable; however, ASD children may be under-diagnosed and/ or undertreated for allergic and other common childhood diseases, in part due to their impaired communication skills. Practicing physicians should be aware of the potential impact of allergic diseases on behavioral symptoms and cognitive activity in ASD children.” (Jyonouchi et al., 2010)

**Pediatricians taking care of toddlers with atopic dermatitis** should have knowledge of this increased risk of developing ADHD and ASD later in life, especially when children have certain comorbidities such as allergic rhinitis, allergic conjunctivitis, and asthma...Children from the atopic dermatitis group with 3 comorbidities together, namely, allergic rhinitis, allergic conjunctivitis, and asthma, had the greatest risk of developing ADHD and ASD.” (Lee et al. 2016)

Allergic diseases such as atopic dermatitis and allergic rhinitis have been linked to abnormalities in the hypothalamus-pituitary-adrenal (HPA) axis (Kaigeromirov et al., 2007). Both adrenaline release via histamine release or direct activation by mast cells have been suggested as possible mechanisms behind this association (Leemann et al., 2011).

Given the high prevalence in ASD of mass-cell overactivation, allergic diseases and non-IgE mediated hypersensitivity reactions, as well as abnormal stress reactivity and dysfunctions in the HPA axis and autonomic nervous system, some of the challenging and odd behaviours that are commonly characterised as ‘autistic behaviour’ could in fact be caused by allergy and intolerance issues. As and when a person with ASD presents with features such as agitation, irritability, aggression, anxiety, sleep difficulties, lack of concentration, hyperactivity and daytime fatigue, allergic and/or non-IgE hypersensitivity should be ruled out.

“Allergic irritability syndrome is a concise, quantifiable way to define the decreased ability to concentrate, bouts of irritability and temper tantrums that sometimes occur as side effects of allergic rhinitis.” (Klein et al., 1985)

**Immunity and inflammation in ASD: Improving long-term outcomes by translating research into clinical practice**

Activation of the immune system is known to lead to structural and functional changes in both central and autonomic nervous systems and impact on behaviour. Prolonged peripheral inflammation causes ‘sickness behaviours’, characterised by reduced affectation and social motivation, repetitive behaviours, avoidance of novel situations, increased anxiety, reduced exploration, self-imposed dietary restrictions and many other symptoms that closely mirror those seen in ASD (Kohman et al., 2009; Patterson, 2012; Yee and Prendergast, 2011).

Experimental studies clearly show that correcting immune abnormalities in post-exposure animals with immune-modulatory treatments results not only in normalisation of their immune function, but also more importantly leads to improvements in cognitive function and reversal of autism-related symptoms and behaviours (Hisao et al., 2012; Kropis et al., 2004; Naviaux et al., 2014).

“Modeling the epidemiological association between prenatal immune challenge and altered brain and behavioral development in rodent systems has produced an astonishing amount of experimental data supporting a role of immune mediated neurodevelopmental abnormalities in major psychiatric illnesses.” (Meyer, 2014)

Small scale human trials and published case studies indicate that addressing the immunological differences found in ASD has the potential to alleviate some of the core symptoms in at least a subgroup of affected individuals (Boris et al., 2007; Chez and Guido-Estrada, 2010; Chez et al., 2012; Duffy et al., 2014; Lv et al., 2013; Matarazzo, 2002; Ramirez et al., 2013; Sandier et al., 2000; Stubbs et al., 1986). One example is treatment with intravenous immunoglobulin (IVIG), which results in a temporary but almost complete amelioration of autistic symptoms in a small subset of individuals (Connery et al., 2018; DiCicco, 2020; Melamed et al., 2018; Plioplys, 1998).

**Gastrointestinal comorbidities and abnormal bacterial flora in ASD**

Gastrointestinal (GI) disorders are seen more frequently in both children and adults with ASD compared with the general population (Leffes et al., 2019; McElhanon et al., 2014). Individuals with ASD frequently suffer with issues of constipation, diarrhoea, gastroesophageal reflux, and inflammatory bowel diseases (Lee et al., 2016). Various other clinical and pathological findings also significantly represented in ASD include increased intestinal permeability (often referred to as a ‘leaky gut’ or ‘gut hyperpermeability’), digestive enzyme deficiencies, bacterial dysbiosis, gastritis, coiltis esophagitis, duodenitis and lymphoid nodular hyperplasia (de Magistris et al., 2010; Hughes et al., 2018; Kushak et al., 2011; Williams et al., 2011). Some clinicians and researchers have suggested that the gastrointestinal inflammation abnormalities identified may be unique to ASD (Horvath et al., 1999; Torrente et al., 2004; Walker et al., 2013).

There is a strong correlation between the severity of GI disorders and the severity of ASD, as well as between the severity of GI symptoms and the...
increased incidence of problem behaviours such as sensory over-responsivity, dysregulated sleep, rigid-compulsive behaviours, aggression, anxiety and irritability (Adams et al., 2011; Peters et al., 2014; Prosperi et al., 2019). Contrary to commonly-held beliefs, the presence of GI dysfunction in children with autism is not associated with any distinct dietary habits or medication use. Parental or guardian reporting of any GI dysfunction in their children is highly concordant with later clinical diagnosis of that dysfunction (Gorrindo et al., 2012).

“Unrecognized gastrointestinal disorders, especially reflux esophagitis and disaccharide malabsorption, may contribute to the behavioural problems of the non-verbal autistic patients.” (Horvat et al., 1999)

A consensus paper published in the journal of the American Academy of Pediatrics (AAP) recommends that health care providers should be alerted to the potential behavioural manifestations of GI disorders in people with ASD, “as these can be atypical and evident only as a change in behaviour, thus presenting a significant challenge to both parents and health care providers.” (Furuta et al., 2012). This paper identified that in children with ASD, subtle or atypical symptoms may indicate the presence of functional GI issues such as constipation. The paper further argues that screening, identification, and treatment of the underlying causes of constipation is appropriate. In individuals with autism, atypical presentations of common GI problems can include the emergence of seemingly non-related ‘autistic’ symptoms such as self-harm, irritability, aggression, strange posturing or movements (Buie et al., 2010).

“Chronic gastrointestinal dysfunction was prevalent...in this cohort. The symptoms of the GI dysfunction were associated with sleep disorders and food intolerance. Thus, it is important to consider such an association when evaluating and treating these commodities.” (Kang et al., 2014)

In another paper published in the journal Pediatrics, the need for appropriate investigations was similarly highlighted: “Despite the magnitude of these issues, potential GI problems are not routinely considered in ASD evaluations. This likely reflects several factors, including variability in reported rates of GI disorders, controversies regarding the relationship between GI symptoms and the putative causes of autism, the limited verbal capacity of many ASD patients, and the lack of recognition by clinicians that certain behavioral manifestations in children with ASDs are indicators of GI problems (e.g. pain, discomfort, or nausea). Whether GI issues in this population are directly related to the pathology of autism, or are strictly a comorbid condition of ASD remains to be determined, but clinical practice and research to date indicate the important role of GI conditions in ASDs and their impact on children as well as their parents and clinicians.” (Coury et al., 2012).

“Our results suggest that clinicians should screen for constipation and diarrhoea or under/over-staining symptoms in children with ASD who have prominent rigid-compulsive symptoms.” (Peters et al., 2013)

The research focus has more recently shifted to the biological correlates underpinning such GI problems. One area of increasing interest is the role played by the gut microbiota. Urinary output of gut flora metabolites as well as analyses of stool and biopsy microbiota samples have consistently demonstrated a range of abnormalities in ASD that could account for the overt clinical GI manifestations (Ming et al., 2012; Yap et al., 2010). Endotoxaemia—the gut microbiota release chemicals that cross the barrier and enter general circulation—has been observed in individuals with ASD. The levels of bacterial toxins in the blood have also been found to correlate with the severity of autism symptoms (Emaurelle et al., 2010). Research into human gut microbiome has led to the proposal that rebalancing the gut flora could offer new treatment avenues for ASD. Evidence continues to emerge in support of the use of pre- and probiotics, antibiotics, and Microbiota Transfer Therapy for the management of challenging behaviours as well as for reducing the core symptoms of ASD (Kang et al., 2020; Ng et al., 2019; Sandler et al., 2000) (also see section ‘Metabolic abnormalities, acquired mitochondrial dysfunction and oxidative stress in ASD’). Transplanted gut microbiota from human donors with ASD into germ-free experimental animals has been shown to induce various hallmark autistic behaviours, namely reduced vocalisation, reduced exploratory behaviour, increased anxiety and increased repetitive behaviours. Colonising the GI tract with bacteria sampled from ASD individuals is already being changes in brain function, as seen by functional brain imaging, and to changes in the expression of ASD-relevant genes in those animals. Such studies elegantly demonstrate the importance of the gut-brain axis and its relevance to ASD (Sharon et al., 2019).

“During subsequent office visits, the patient communicated a strong desire to continue treatment due to improvements in his health and quality of life. For this patient, repeated treatment with antibiotics greatly improved gastrointestinal function, decreased reported bowel pain, and reduced aggressive and self-injurious behaviours.” (Ramirez et al., 2013)

As previously discussed, pain and sickness have profound influences on mood, cognition, and behaviour, including sociality and communication. Equally, chronic inflammation and infections of the GI tract are associated with increased circulatory levels of pro-inflammatory cytokines which also seem to have direct effects on behaviour, including anxiety, motivation, socialisation, avoidance of novel situations, and adherence to routine and repetitive actions. Metabolites derived from the microbiota and immune mediators interact with the endocrine and peripheral neural pathways and consequently modulate brain function (Cryan and Dinan, 2012; Goethe et al., 2005; Sharkey and Keesoe, 2001). Gastrointestinal imbalances, such as Small Intestinal Bacterial Overgrowth (SIBO) are also known to affect normal brain functioning and induce anxiety and aberrant behaviours. These effects are mediated via the enteric nervous systems and the vagus nerve, and via dysregulation of the HPA axis, all of which have been reported as atypical in autism (Diaz Heizet et al., 2011; Foster and McVey Neufeld, 2013) (also see section ‘Dysfunction of the autonomic nervous system and hypothalamic-pituitary-adrenal axis in ASD’). In animal models of autism, animals exposed early in life to bacterial toxins can develop long lasting autistic traits (Baharonnor et al., 2012; MacFabe et al., 2011; Willette et al., 2011) which can be largely reversed by changing the composition of gut bacterial flora (Hsiao et al., 2013; Kim et al., 2013).

Health professionals should consider the possibility of GI dysfunction being present in patients with ASD, especially in those presenting with strange posturing or movements, sleep disorders, food intolerances, and unexplained aggressive or self-injurious behaviours.

“Emerging concept of a microbiota–gut–brain axis suggests that modulation of the gut microbiota may be a tractable strategy for developing novel therapeutics for complex CNS disorders.” (Cryan, 2012)

If the gastrointestinal disorder is recognized and medical treatment is effective, the problem behaviours may diminish. When abdominal pain or discomfort is a setting event, psychotropic medications are likely to be ineffective and may even aggravate the problem.” (Buie et al., 2010) ‘Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASD: a consensus report.’

**Non-coeliac gluten sensitivity and ASD**

Dietary interventions involving the exclusion of gluten (a protein found in wheat and various other cereal grains) and/or casein (a protein found in mammalian milk and dairy sources) are often adopted in autism research and practice. Many parents have reported beneficial changes to their child’s symptoms following the removal of these foods (Whiteley et al., 2010). Lay observations have been followed by early preliminary research (Gooch et al., 1971) and published case reports on dietary changes leading to improvement in some ASD-related symptoms and behaviours (El-Rashidy et al., 2017; Herbert and Buckley, 2013). In a 2014 survey conducted by Thinking Autism of families with ASD (n=304) nearly 90% of respondents...
had tried dietary changes for their child with ASD, with 94% of those reporting improvements as a result, and less than 1% reporting worsening of symptoms or behaviours. Of those reporting improvements, 30% characterised those as “life-changing” (Thinking Autism, 2014). While conclusive enzymes, such as lactase and disaccharidases, has also been observed in ASD, and may be behind the inability to digest and/or absorb some foods, as well as reported positive response to exclusionary diets in some individuals (Horvath et al., 1999; Kushak et al., 2011; Williams et al., 2011). Screening for gluten-related conditions such as coeliac disease (CD) symptoms are present. It should be noted that Carroccio and colleagues (2012) found that the main histological characteristic of NCGS was mucosal eosinophil infiltration. Histological findings of prominent mucosal eosinophil infiltration have been observed in a high percentage of children with ASD and appear to be significantly lower in children following a gluten-free diet (Ashwood et al., 2008; Chen et al., 2009).

“The findings indicate that the observed antigliadin immune response in patients with autism is likely to involve a mechanism that is distinct from celiac disease” (Lau et al., 2013)

Outside of cases fulfilling both the serological and histological criteria for a diagnosis of coeliac disease, evidence is emerging for a NCGS variant present in some people with ASD. Ludvigsson et al. (2011) reported on the presence of positive coeliac disease serology but with a normal gut mucosa in cases of ASD. Other groups have reported similar findings in relation to immune reactivity to gluten in de Magistris et al., 2013; Lau et al., 2013. Such results also overlap with other data suggestive of impairment of the gut barrier (intestinal hyperpermeability) in some cases (de Magistris et al., 2010). Of particular interest to some cases (de Magistris et al., 2010). Of particular interest to some cases (de Magistris et al., 2010). Of particular interest to some cases (de Magistris et al., 2010). Of particular interest to some cases (de Magistris et al., 2010). Of particular interest to some cases (de Magistris et al., 2010). Of particular interest to some cases (de Magistris et al., 2010).

Nutritional abnormalities, acquired mitochondrial dysfunction and oxidative stress in ASD

Compared with children and adults in the general population, those with ASD are at a significantly higher risk for presenting with obesity or weight issues (Zheng et al., 2017). This risk also seems to correlate with the severity of autism and the occurrence of a number of metabolic disorders including hypertension, diabetes and dyslipidemia (Oren et al., 2015; Fortuna et al., 2016). It should be noted that the increased weight gain has also been recorded in the younger age group of 2-5 years old with ASD (Hall et al., 2015). Such findings are at odds with the typical trend of obesity being more prevalent the older the child becomes. It also suggests that the reason(s) behind weight gain in ASD may involve intrinsic biological factors, counteracting commonly held assumptions that high obesity rates in ASD are solely due to poor eating habits, medication practices or a lack of physical activity (Dhaliwal et al., 2019). Such findings are also consistent with scientific observations finding maternal obesity and metabolic disorders to be a significant risk factor for ASD (Sanchez et al., 2018; Wang et al., 2016; Xu et al., 2014). Interestingly, and in common with autism, obesity has also been linked to a dysregulated gut microbiota (Delzenne et al., 2011), pointing to potential common underlying causes or pathways.

“Our findings … suggest that individuals with ASD should undergo evaluation for mitochondrial dysfunction, as novel and promising treatments are under development for mitochondrial disorders.” (Goh et al., 2014)

There is now substantial evidence showing that impaired energy metabolism and mitochondrial dysfunction, including brain energy metabolism, perturbation in sulphur and amino acid metabolism, high levels of oxidative stress and impaired methyltransferase pathways are more common in persons with ASD than other groups (Goh et al., 2014; Weissman et al., 2008), and could play a pathological role in at least a subset of people with the condition (Rose et al., 2018). Furthermore, levels of oxidative stress and mitochondrial dysfunction have been found to correlate strongly with the severity of ASD (Alabdali et al., 2014).

Elevations in oxidative stress, reduced levels of glutathione and other cellular antioxidants, as well as increased levels of several toxic metals and other environmental toxicants, have been found in many cell types and various areas of the body, including cells of the immune system such as leukocytes.
Although genetic factors also play an important role, they are of substantially lower magnitude than estimates from prior twin studies of autism. Our study provides evidence that the rate of concordance in dizygotic twins may have been seriously underestimated in previous studies and the influence of genetic factors on the susceptibility to develop autism, underestimated.

Halmeyer et al., 2011 ‘Genetic penetrability and shared environmental factors among twin pairs with autism’

CASE EXAMPLE 10
Maryam is a 4-year-old girl with regressive autism. At presentation she suffered frequent night waking, episodic distress and, on direct questioning, posturing behaviour. Stools were malodorous, variable in consistency and could cause some discomfort. Developmentally, Maryam had a few words and was making slow progress. Mum felt the slow progress was due to her being in some sort of pain, and not sleeping properly. On examination, she looked uncomfortable. She was pale, with dry skin. There was slight right iliac fossa tenderness. Bloods revealed an Erythrocyte Sedimentation Rate of 45 and iron deficiency anaemia. She was referred to a tertiary gastroenterologist who advised a gluten, casein and soya free diet. Symptoms improved significantly. She began sleeping through the night, passing normal bowel motions and looked brighter. Speech and general development improved. ESR fell to 25 after 2 months, 19 after 4 months and after one year reached 9.

(Chauhan et al., 2012; Ghezzo et al., 2013; Gu et al., 2013; Rossignol and Frye, 2014a; Rossignol et al., 2014b). Relevant to those observations are findings of deficiencies in the way gastrointestinal bacteria degrade environmental toxins in ASD individuals compared to controls. These microbiome ‘deficiencies’ have been found to strongly correlate with the degree of mitochondrial dysfunction as well as the severity of ASD symptoms, raising a possibility that impairments in microbiome-linked detoxification pathways may be involved in the development and/or severity of ASD (Zhang et al., 2020).

A substantial percentage of individuals with ASD display markers of abnormal mitochondrial energy metabolism, such as elevated lactate, pyruvate and alanine in blood, urine and/or cerebrospinal fluid, as well as serum carnitine deficiency (Filipek et al., 2004; Hollis et al., 2017; Olivera et al., 2005). In the majority of cases these abnormalities are not linked to genetic causes or other primary inborn errors of metabolism, as these conditions are often related to metabolic and chemical abnormalities observed in ASD are instead thought to be consequences of immune dysfunction (Palmeri and Persico, 2010; Rose et al., 2014) or the aforementioned disturbances in the microbiome (Kang et al., 2020; Ming et al., 2012; Wang et al., 2012; Zhang et al., 2020) rather than inherited genetic abnormalities. In other words, they have the characteristic of being influenced by the environment.

Conversely, autistic features may be a leading or sometimes the only visible clinical feature of the more ‘classic’ types of genetic metabolic diseases such as urea cycle disorders, inborn errors of biotin or purine metabolism (Mayatepek, 2010) or creatine transporter deficiency (Yildiz et al., 2020; Yoganathan et al., 2020). Abnormal cholesterol synthesis can also have autism as a presenting feature, and in some cases improvements in ASD-related behavioural symptoms are noted following normalisation of cholesterol metabolism (Calvo et al., 2014; Diaz-Stransky et al., 2012).

Cerebral folate deficiency, together with the presence of folate receptors autoantibodies, have also been reported to play a pathological role in at least some cases of ASD (Kralíčková et al., 2017). Both of these conditions are significantly increased in ASD compared to controls. The folate deficiency and metabolic abnormalities observed in ASD are instead thought to be consequences of immune dysfunction (Palmeri and Persico, 2010; Rose et al., 2014) or the aforementioned disturbances in the microbiome (Kang et al., 2020; Ming et al., 2012; Wang et al., 2012; Zhang et al., 2020) rather than inherited genetic abnormalities. In other words, they have the characteristic of being influenced by the environment.

NAC in particular seems to be a promising avenue for reducing irritability, hyperactivity and increasing social awareness (Lee et al., 2020) or self-injurious behaviour (Marler et al., 2014) in some individuals with ASD. Tetrahydrobiopterin (BH4) has been shown as very encouraging results, with statistically significant improvements noted across domains such as social awareness, autism manners, hyperactivity, and inappropriate speech (Frye et al., 2013a; Kliman et al., 2013). In addition to improving some of the aberrant behaviours associated with autism, treatments such as NAC have the potential to address physical abnormalities such as muscle weakness or motor impairments, shown to be correlated with severity of autism (Kern et al., 2013; Macdonald et al., 2014). One study to date applied the ‘precision-medicine’ approach, and initial investigation of metabolic biomarkers in 187 children uncovered abnormalities in 13 of the study subjects. Both supplementation and ketogenic diet were introduced based on individual findings, resulting in mild to significant clinical improvement in ASD symptoms in those 13 individuals (Splioti et al., 2013). A recent study investigated the effects of the novel therapy known as microbial transfer therapy, in which gut microbiota from healthy donors are transplanted into patients. The procedure produced not only significant and lasting changes in both gastrointestinal and behavioral symptoms and ASD-related functional impairments, but also a marked normalisation of key blood metabolites in children with ASD (Kang et al., 2020) (also see section ‘Gastrointestinal comorbidities and abnormal bacterial flora in ASD’).

Health professionals should be aware of metabolic and mitochondrial dysfunction being present and contributing to autism aetiology in some patients with ASD, even in the absence of primary inborn errors of metabolism or mitochondrial disease.

Seizure disorders in ASD
The prevalence of seizure disorders in ASD is significantly higher than in the general population. An estimated 20% of individuals with ASD develop epilepsy at some point in their life (Besag, 2017). Subclinical epileptiform activity, in the absence of clinic seizures, is also more prevalent (Jasken et al., 2012; Levine et al., 1999; Muñoz-Yunta et al., 2008).

“The reduction in aberrant behaviors observed in this series suggests that some behaviors previously attributed to autism may be associated with intractable epilepsy.” (Kokoszka et al., 2017)

While an association between the more severe forms of ASD and epilepsy has been known about for many years (Kö et al., 2016), more recent investigations have shown that individuals with so-called high-functioning ASD/Asperger Syndrome are also at increased risk of developing epilepsy and/or presenting with EEG (electroencephalogram) abnormalities (Ertürk Çetin et al., 2017). Conversely, the rates of ASD and other neurodevelopmental disorders are also significantly higher among individuals with epilepsy compared with the general population (Strasser et al., 2018). Epilepsy and autism should be seen as symptoms of specific pathologies rather than merely diagnoses. Because of their correlation it is proposed that both conditions may share similar underlying pathophysiology, such as autoimmune, infection and/or brain inflammation (Choi and Koh, 2008; Ong et al., 2014; Spann et al., 2019). Notably, in maternal infection animal models of autism, emergence of both autism-related symptoms and epilepsy (or EEG abnormalities) can potentially be prevented by avoiding or blocking major inflammatory mediators (Carlezo et al., 2019; Sankar et al., 2014).

“Given the frequency of seizure disorders in (ASD) population, a high index of clinical suspicion should be maintained for subtle symptoms of seizures.” (Kagan-Kushnir et al., 2005)

Epilepsy is a major contributing factor to the elevated early mortality risk seen in ASD, making detection and treatment of this medical comorbidity of the utmost importance (Mouridsen et al., 2011; Woollenden et al., 2012). When epileptiform activity is present, interventions aimed at its control can sometimes lead to a corresponding improvement in the general population. An estimated 20% of individuals with ASD develop epilepsy at some point in their life (Besag, 2017). Subclinical epileptiform activity, in the absence of
“When epileptiform activity is present, medical therapy designed at ameliorating the epileptiform activity may lead to an improvement in autistic features.”

Lewine 1999 et al., “Magnetoecephalographic patterns of epileptiform activity in children with regressive autism spectrum disorders”

in language, cognition and ASD-related symptoms and behaviours, alongside a reduction in seizure activity. Antiepileptic medication such as levetiracetam (Wang et al., 2017), phenytoin (Bird, 2015), valproate and various other medicines (Garcia-Peñas, 2005) have been reported to bring about improvements in core ASD symptoms.

“Epilepsy and autoimmune disease frequently cooccur; patients with either condition should undergo surveillance for the other. The potential role of autoimmunity must be given due consideration in epilepsy so that we are not overlooking a treatable cause.” (Ong et al., 2014)

There is preliminary evidence that a ketogenic diet, which has been widely and successfully used for controlling or ameliorating a broad spectrum of seizure types, reduces the symptoms of ASD in some people (Mu et al., 2020; Żańczowska et al., 2018). Parallel studies have also shown there is an association between Coeliac Disease (CD), epilepsy and cerebral calcifications; a gluten exclusion diet can in some cases improve cognition and autistic traits (Pennisi et al., 2017) and/or reduce hyperactivity, anger outbursts, aggression, self-harm and social impairments (Capa et al., 2018; Milovanovic et al., 2018; Nicotera et al., 2019). Apart from their potential to negatively impact cognitive and executive function, long term studies have revealed that over 20% of people with ASD presenting with abnormal IEDs convert to clinical seizures (Veerapen et al., 2018).

For those individuals with ASD who exhibit unusual behaviour—for example, sudden and unprovoked outbursts of aggression, irritability, crying, screaming or self-harming, unusual facial and body movements and posturing, staring spells, covering of ears—an EEG should be considered for ruling out seizure activity (Kokoszka et al., 2017; Shuper and Milamori, 1995). Various findings support the routine diagnostic use of EEG with individuals with ASD (Swatzyna et al., 2017). Several groups have stressed the importance of EEG recording in sleep, which can show significantly higher sensitivity for epileptiform discharges in ASD compared to awake-state readings (Milovanovic et al., 2018; Nicotera et al., 2019).

Motor dysfunction, connective tissue disturbance and movement disorders in ASD

A large proportion of individuals with ASD present with motor dysfunction issues (Bell et al., 2019). Some of the earliest publications on ASD include discussion on motor abnormalities (Kanner, 1943). Recent studies have uncovered strong correlations between fine and gross motor skills dysfunction and the degree of cognitive and functional impairments in individuals with ASD (Bal et al., 2020; Kaur et al., 2018). Hypotonia (low muscle tone) is a common motor symptom noted in some studies, thought to affect over 50% of individuals with ASD (Ming et al., 2007). Hypotonia also seems to improve with age. In the same study group of 154 children with ASD, Ming et al reported that dyspraxia (dysfunction in motor planning), which can affect gross, fine and oral motor skills is seen in approximately 30% of children with ASD, improving with age. Issues with walking were observed in approximately 20%, and gross motor delays in about 10% of their cohort. Ehlers-Danlos Syndrome, a connective tissue disorder characterised by joint hypermobility and GI symptoms amongst other manifestations, has also been reported alongside ASD (Cederlöf et al., 2016). It is thought that motor dysfunction could be related to frontal-striatal and cerebellar abnormalities, although the relationship between ASD and motor function is largely under-researched (Nayate et al., 2005).

“Our study findings highlight the need for clinicians and therapists to include motor evaluations and interventions in the standard-of-care of children with ASD and for the broader autism community to recognize dyspraxia as an integral part of the definition of ASD.” (Kaur et al., 2018)

Sensory dysfunction and abnormal pain reaction in ASD

Sensory processing dysfunction is another important feature of ASD, covering all of the primary senses—auditory, visual, tactile, olfactory, proprioceptive, vestibular and gustatory. A large body of scientific literature describes differences in the sensation and/or processing of sensory information in ASD (Baum et al., 2015). More recent investigations have also uncovered peripheral nerve degeneration with reduced nerve fibre density in over half of individuals with ASD (Chien et al., 2020). Some of the more challenging behaviours associated with ASD appear to be causally linked to sensory dysfunctions and the abnormal processing of pain (Goldschmidt, 2017; O’Nions et al., 2018; Tudor et al., 2015).

“Given the extreme heterogeneity of ASDs and other neurodevelopmental disorders, effective treatments for individuals with ASDs will likely benefit from a personalized medicine approach that takes into account individual differences in etiologic and phenotypic characteristics.”


Dysfunction of the autonomic nervous system and HPA axis in ASD

The autonomic nervous system is a component of the peripheral nervous system that regulates involuntary physiologic processes such as heart rate, blood pressure, respiration, digestion. It contains three anatomically distinct divisions: sympathetic, parasympathetic and enteric. The sympathetic system directs rapid body reactions to dangerous situations. The parasympathetic system conserves energy, reduces the heart rate, relaxes sphincter muscles in the GI tract, stimulates intestinal and gland activity. The enteric system is composed of an extensive web of neurons (100 millions) and is chiefly responsible of the regulation of the digestive system.

Individuals with ASD exhibit pronounced and exaggerated fight-or-flight sympathetic stress responses. They seemingly overreact to triggers from the environment and are unable to control their reactions, which may be frightening for them and the people around them. This can lead to a cycle of avoidance, worsening anxiety and further withdrawal. Over three years he was trialled on various neuroleptics, to no effect. He was trialled on sertraline, to severe autism. He presented with sudden onset self-harm and destructive behaviour. Over three years he was trialled on various neuroleptics, to minimal effect. Chest infections had become progressively worse over the three-year period. Chest exam suggested right lower consolidation. Chest CT revealed consolidation. Only partial resolution with antibiotics was achieved. Bronchoscopy revealed a 15mm twig central to the consolidation. Removal, prednisolone and a protracted course of azithromycin resolved the consolidation, and his self-harm and destructive behaviour also resolved. Christopher had not localised to the pain source nor had he developed pyrexia.

CASE EXAMPLE 11

Christopher is a 20-year-old male with moderate to severe autism. He presented with sudden onset self-harm and destructive behaviour. Over three years he was trialled on various neuroleptics, to minimal effect. Chest infections had become progressively worse over the three-year period. Chest exam suggested right lower consolidation. Chest CT revealed consolidation. Only partial resolution with antibiotics was achieved. Bronchoscopy revealed a 15mm twig central to the consolidation. Removal, prednisolone and a protracted course of azithromycin resolved the consolidation, and his self-harm and destructive behaviour also resolved. Christopher had not localised to the pain source nor had he developed pyrexia.

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disappearance of any perceived threat. Studies have also reported alterations in heart rate and heart rate variability (Bazelmans et al., 2019; Thapa et al., 2019), mean arterial and diastolic blood pressure, atypical pupillary light reflex and atypical autonomic response to anxiety (Anderson et al., 2013; Cheshire, 2012; Kushki et al., 2013; Patirquin et al., 2011). Indications of abnormal activation of the sympathetic nervous system such as raised plasma noradrenaline and high urinary vanillylmandelic acid have also been found (Bharath et al., 2019; Lake et al., 1977). Furthermore, findings of lower baseline respiratory sinus arrhythmia have been reported, suggesting a reduced vagal modulation in ASD (Bai et al., 2010).

HPA axis is an interactive neuroendocrine unit comprising the hypothalamus (located in the brain), the pituitary gland (located at the base of the brain), and the adrenal glands (located on the top of the kidneys). The HPA axis plays key roles in basal homeostasis and in the body’s response to stress. The major pathway of the axis results in the production and secretion of cortisol.

Widespread abnormalities in the functioning of the HPA axis have been observed in ASD. Abnormal levels of anterior pituitary hormone, adrenocorticotropic hormone and significantly elevated levels of cortisol following stress conditioning, including a prolonged duration of cortisol secretion recovery, are significant findings in individuals with ASD compared to asymptomatic controls (Corbett et al., 2010; Cunin et al., 2003; Iwata et al., 2011; Spratt et al., 2012). This heightened arousal mode and hyper-responsivity to stress in individuals with autism correlates with deficiencies in adaptive functioning and use of language, and may possibly cause or exacerbate many of the additional problems frequently present in individuals with autism, such as anxiety, avoidance of novel situations, rigid and/or challenging behaviours such as aggression and self-harm. Ongoing exposure to high cortisol is known to negatively impact both physical and mental health. Chronic dysregulation of the HPA axis in response to stress, as is seen in autism, can have neurotoxic effects, and is potentially predisposing to several other mental and health disorders. The rates of major depression and suicide are, for example, significantly increased in autism.

Immune-related factors such as chronic inflammation and heightened allergic reactivity, or factors related to gastrointestinal dysbiosis and microbial translocation in ASD, as previously discussed, offer biologically plausible explanations for observed dysregulation of the HPA axis (de Theije et al., 2014; Liebmann et al., 2011; Voris et al., 2017). Autonomic and HPA dysfunction are capable of influencing the behavioural symptoms of ASD and may contribute to socio-emotional deficits (Eilam-Stock et al., 2014). Targeting autonomic dysfunction therefore constitutes a treatment avenue for some of the debilitating symptoms, such as heightened anxiety, lack of emotional regulation as well as improving cognitive and verbal functioning (Beversdorf, 2020; Ming et al., 2008).

CASE EXAMPLE 12
Ivan is a 5-year old boy with regressive autism. He developed normally as a baby, including normal speech (bilingual) development. He started presenting with unusual behaviours at 18 months, including tip-toe walking, hand flapping, motor stereotypes. Lost previously acquired speech. Diagnosis of autism received at 1 year and 9 months. Ivan's gastrointestinal problems started around 24 months of age. Stools started to become mushy, malodorous, and light in colour. Ivan suffered from recurrent Herpes infection on the hands, causing permanent scarring. Recently Ivan presented with an acute onset of irritability, hyperactivity, sleep disturbance and occasional incontinence. His obsessional behaviours were marked. He was seen by rheumatology consultant, who undertook bloods. ASOT and Anti-DNAse B were positive. He was duly commenced on co-amoxiclav and his new symptoms resolved rapidly. Ivan's speech improved, and he became more socially engaged. He is currently under the care of rheumatology for PANDAS, and is reported as doing well.

Conclusion
Children and adults with ASD have an increased need for paediatric and/or specialist services, both for their core functional deficits and concurrent medical conditions. There is now a large body of research underscoring the increased risk for individuals with a diagnosis of ASD to be suffering from immune dysregulation, allergies, food sensitivities, various gastrointestinal disorders, excessive oxidative stress, mitochondrial and metabolic dysfunction, autonomic disturbances, subclinical seizure activity and frank epilepsy. Research shows that the increased severity of many of these conditions correlates with the increased severity of symptoms of ASD. Such comorbidities can also be more difficult to recognise. The failure to identify medical conditions can be due in part to communication impairments and sometimes ambiguous symptomatology, but widespread underdiagnosis and barriers to accessing appropriate health care for people with ASD can also play a role. The commonly but erroneously held assumption that aberrant behaviours and symptoms are ‘just a part of autism’ also plays a part. Diagnostic overshadowing leaves pathologies untreated, clearly results in health inequalities and constitutes a gross injustice to the individual and their loved ones.

It is of the utmost importance to raise awareness of current research into medical comorbidities and underlying conditions in ASD among healthcare professionals and policy makers, as well as parents and carers, in order to provide appropriate health care and support to individuals with ASD. Without increased awareness and consequent improved investigations into and treatment of physical health problems, people with ASD will continue to experience clear health inequalities and decreased quality of life. Increasingly, research is also showing that appropriate treatment of these conditions can ameliorate the symptoms used to diagnose ASD. Given the growing neurological, immunological, metabolic, and endocrinological evidence that ASD is, at least for a subset of individuals, a whole body disorder, receipt of what is currently a fully behavioural diagnosis should represent the beginning of medical investigation and assessment, not the end.
Approaching comorbidity in the ASD patient: Medical considerations

The behavioural features that characterise ASD rarely present in a diagnostic vacuum. There is overwhelming scientific evidence that many physical comorbidities can and do accompany a diagnosis of ASD and can have a profound effect on quality of life. Identifying, diagnosing and addressing the root causes of the various physical comorbidity issues potentially associated with ASD can be life-changing.

There are however numerous challenges to such endeavours; not least that individuals with ASD are often affected in their communication, self-awareness and pain perception. This means that many people with ASD cannot simply tell a doctor or other healthcare professional where and what they are suffering from. It is more likely that any physical health problems concurrent to ASD will manifest through the behaviour a person displays.

Understanding the biology of ASD requires different fields of science and medicine to work together in an integrated fashion. The views of parents and/or caregivers, who are closest and often most informed of the day-to-day health of the individual with ASD, are an important part of that integrated approach, despite potentially being at risk of being dismissed because what they report may not fit the ‘ASD picture’ as is currently understood. Organisational constraints, meaning healthcare professionals often do not have the time to understand in detail the condition their patients suffer from in a routine appointment, reflect another potential barrier to tackling physical comorbidity issues accompanying ASD.

This review presents some of the evidence for the presence of physical health issues accompanying ASD and aims to progress the way ASD is widely understood by many groups as an initial step to setting a path for possible remedial interventions. We want to highlight the following points to be taken into account to enable accurate diagnosis:

- Problem behaviour in people with ASD may be the primary or sole symptom of an underlying medical condition, which can be acute or chronic, progressive or static.
- Features such as self-harming, aggression, night-waking, change in appetite, grimacing and strange postures are definitively not part of the diagnostic criteria of ASD. As evidenced by current research and accumulating clinical experience, these and other symptoms and behaviours should not be automatically attributed to either mental health or behavioural problems, or dismissed as inherent to ASD or some preconceived facet of that diagnosis. There is a substantial body of evidence that these behaviours have physical origins and to prevent diagnostic overshadowing, organic explanations should always be sought.
- Parents and carers generally do give accurate and quality information about symptoms or behaviour change in their charges. Parents and carers may however be unaware of the possible implications of the symptomatology, especially if at any point they have been told that behaviours are ‘simply autism’.
- Individuals with ASD who are experiencing pain or discomfort may not be able to identify the physical location of that pain/discomfort within their body.
- Individuals with ASD may not respond in the typical way to common illnesses.

In order to avoid premature attribution of physical health issues to the ASD phenotype and the consequences thereof, all of those with a vested interest in the health of individuals with ASD—professionals, parents, and carers—need to be informed of the following possible issues:

### Behaviours that may indicate an underlying illness, pain or discomfort, include:

- Loss of previously acquired skills
- Sudden change in behaviour
- Irritability and low mood
- Tantrums and oppositional behaviour
- Frequent night-waking or general sleep disturbance
- Teeth grinding
- Change to appetite or dietary preferences
- Heightened anxiety and/or avoidance behaviours
- Tapping or touching behaviour (e.g. finger tapping on throat)
- Sensory hyper-responsivity: hyperacusis, tactile defensiveness, sensitivity to light
- Walking on toes
- Covering ears with hands
- Posturing or seeking pressure to specific area
- Behaviour around evacuation
- Aggression: onset of, or increase in, aggressive behaviour
- Facial grimacing or brow furrowing, tics
- Self-injurious behaviour: biting, hitting/slapping face, head-banging, unexplained increase in self-injury
- Sensory hyper-responsivity: hyperacusis, tactile defensiveness, sensitivity to light
- Constant eating/drink/ swallowing (‘grazing’ behaviour)
- Frequent clearing of throat, swallowing
- Mouthing behaviours: chewing on clothes
- Repetitive rocking or other new repetitive movement
- Sobbing ‘for no reason at all’
- Vocal expressions: moaning, groaning, sighing, whining
- Agitation: pacing, jumping up and down
- Blinking, sudden screaming, spinning and fixed look

### Medical conditions underlying pain and discomfort can be acute or chronic, progressive or static.

### Common medical conditions known to cause behavioural symptoms in ASD include, but are not limited to:

- Headache
- Earache
- Musculoskeletal injury or disease
- Toothache
- Seizure Disorders and subclinical epileptiform activity
- Soft or hard stool constipation
- Sore Throat
- Reflux
- Oesophagitis
- Gastritis
- Colitis
- Small Intestinal Bacterial overgrowth
- Allergy Disorder (including Non-IgE mediated disorders and food intolerances)
References


Thinking Autism Survey (2014) Thinking Autism. Available through mail@thinkingautism.org.uk


Autism is a whole-body disorder. Changes in behaviour and social communication can occur as a result of systemic and complex disease process, including seizure disorders/epilepsy, allergies and atopic diseases, bacterial and viral infections, severe headaches and migraines, metabolic and heart disease, osteoporosis and gastrointestinal disorders.

Mortality is significantly increased in ASD, with death rates more than three times higher than the general population. The severity of the above-mentioned medical conditions, including epilepsy, and the risk of premature death correlate with the severity of core ASD symptoms.

"Care providers should be aware that problem behavior in patients with ASDs may be the primary or sole symptom of the underlying medical condition." Consensus Report, Pediatrics, Buie et al., 2010

Accurate diagnosis of co-existing medical conditions can be achieved by taking account of the following:
- Problem behaviour may be the primary or sole symptom of an underlying medical condition.
- Self-harming, aggression, night-waking, change in appetite, grimacing, strange postures and such are not part of the diagnostic criteria of autism and should not be erroneously attributed to either a mental health or behavioural problem or dismissed as inherent to autism or some preconceived facet of that diagnosis.
- To avoid diagnostic overshadowing, organic causes should be sought in the first instance.
- Parents and carers generally do give accurate and quality information about symptoms or behaviour change; however, they may be unaware of the possible implications of the symptomatology, especially if at any point they have been told that behaviours are ‘simply autism’.
- Individuals with autism who are experiencing pain or discomfort may not be able to identify the physical location of that pain/discomfort within their body.
- Individuals with autism may not respond in the typical way to common illnesses.

**THE TABLE BELOW IS DESIGNED TO HELP IMPROVE RECOGNITION OF SOME OF THE PROBLEMS ENCOUNTERED WHEN PATIENTS WITH AUTISM PRESENT WITH COMORBIT HEALTH ISSUES.**

<table>
<thead>
<tr>
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**Common sources of pain and discomfort include:**
- Headache
- Earache
- Toothache
- Sore throat
- Reflex
- Drowsiness
- Gastritis
- Constipation
- Soft or hard stool constipation
- Small Intestinal Bacterial Overgrowth
- Musculoskeletal injury or disease
- Seizure disorders and subclinical epilepsy activity
- Allergy Disorder
- Pain can be acute or chronic, progressive or static
“Caring for youths with autism spectrum disorder can be overwhelming for some primary care physicians because of the multiple comorbid conditions that often accompany ASD. But treating these associated health issues often helps children with ASD feel better and can improve their behavior and performance in school.”

Dr James Perrin, Professor of Pediatrics, Harvard Medical School, President–elect of the American Academy of Pediatrics

“This study reveals that medical disorders or manifestations are highly prevalent in children and adolescents diagnosed with ASD. Abnormal clinical neurological findings were quite common, and we found a high degree of pathology as a result of the additional medical investigations. This means that an appropriately extensive medical assessment is essential in all cases.”

Isaksen et al., 2012 ‘Children with autism spectrum disorders — The importance of medical investigations’

“Care providers should be aware that problem behavior in patients with ASDs may be the primary or sole symptom of the underlying medical condition.”

Buie et al., 2010 ‘Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report’

“Many individuals with ASD have symptoms associated with underlying medical conditions, including seizures, sleep problems, gastrointestinal (GI) disorders, psychiatric conditions, nutritional deficiencies, and metabolic conditions; when left untreated, these conditions may not only compromise general health but also have clear effects on behavior, development, and educational outcomes for individuals with ASD.”


“We need to empower primary care physicians to know that they already have the skill set to work with children who have autism... Doctors can address these co-occurring behaviors head-on. It will make a positive difference.”

Darryn M. Sikora, PhD, pediatric psychologist, Providence Child Center

“Autism is what we call a mosaic disease, it has many different facets to it... if you look into the literature, you’ll find that autism isn’t just a sort of neuropsychiatric, behavioural, and social disorder... It is a systemic disease, but the most obvious effect is the social and behavioural, and so it tends to be associated with that... What we have to do now using our modern technology is to take a step back, look at the whole problem as a systemic problem, and see how all the abnormal interactions that are occurring in the different organ systems in the body might impact on brain development and to give us the symptoms of autism, which are becoming all too familiar.”

Prof Jeremy Nicholson, Chair In Biological Chemistry, Head of Department of Surgery and Cancer, Imperial College London

“Sudden and unexplained behavioral change can be the hallmark of underlying pain or discomfort. Behavioral treatment may be initiated as the possible concurrent medical illness is being investigated, diagnosed (or excluded), and treated, but the behavioral treatment should not substitute for medical investigation.”

Buie et al., 2010 ‘Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report’