Bridging the Gap Between Physical Health and Autism Spectrum Disorder

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Abstract: Autism spectrum disorder (ASD) is a highly complex and heterogeneous developmental disorder that affects how individuals communicate with other people and relate to the world around them. Research and clinical focus on the behavioural and cognitive manifestations of ASD, whilst important, have obscured the recognition that ASD is also commonly associated with a range of physical and mental health conditions. Many physical conditions appear with greater frequency in individuals with ASD compared to non-ASD populations. These can contribute to a worsening of social communication and behaviour, lower quality of life, higher morbidity and premature mortality. We highlight some of the key physical comorbidities affecting the immune and the gastrointestinal systems, metabolism and brain function in ASD. We discuss how healthcare professionals working with individuals with ASD and parents/carers have a duty to recognise their needs in order to improve their overall health and wellbeing, deliver equality in their healthcare experiences and reduce the likelihood of morbidity and early mortality associated with the condition.

Keywords: autism spectrum disorder, ASD, physical health, comorbidity, inequality

Plain Language Summary

A diagnosis of autism spectrum disorder (ASD) is based on the presence of impairments with social communication and repetitive or restricted patterns of behaviour. Much of the scientific interest has focused on the behaviours and cognitive functioning that define ASD and how they can affect a person's day-to-day quality of life. However, ASD does not typically appear as a stand-alone condition. Various other health conditions affecting physical and mental wellbeing are also commonly reported. These can have an important impact on daily living, social communication and behaviour. We highlight some of the conditions affecting the immune and gastrointestinal systems, metabolism and brain function, and how they can influence a person's quality of life and increase the risk of early mortality. We discuss how professionals, working with those with ASD and their parents and carers can recognise the impact such conditions may have on individuals with ASD.

Introduction

Autism spectrum disorder (ASD) is a highly heterogeneous and complex neurodevelopmental condition. It is diagnosed by the presence of core deficits in the areas of social communication and restricted and/or repetitive patterns of behaviours that significantly impact on quality of life.¹ There is notable heterogeneity in the presentation of core autistic features, such that ASD for some individuals means a life of constant care and supervision with minimal opportunities for independent living. For others, ASD is associated with many lasting challenges but does not

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hinder the acquisition of independent living skills, meaningful employment and/or the development of close relationships.

ASD is for most people a lifelong disability.² Whilst developmental trajectories vary across individuals as a result of maturation and interventions^{3,4} there is a substantial degree of persistence of core ASD features over a lifetime for many. This means that individualised support provisions are required across the lifespan for most individuals with ASD. The disparities in presentation subsumed under a singular label of ASD have led some to question whether a more plural taxonomy for autism is required⁵ based on differing aetiologies, symptom profiles, responses to intervention and courses.

The current estimated prevalence of ASD is between 1–2%^{6–8} with a trend towards increasing numbers being diagnosed.^{9–12} Importantly, evidence of the increasing prevalence of ASD is not confined to one geographic area^{13,14} but instead reflects an increasing global trend. Various factors have been put forward to account for the increasing number of cases of ASD including a widening of the diagnostic criteria, better case ascertainment, diagnostic substitution and increasing public awareness of the heterogeneity of ASD.^{15,16} A true increase in numbers is also possible.¹⁷

The aetiologies of ASD are highly complex and vary across individuals. In most cases the emergence of ASD likely involves an interplay between genetic and environmental influences.¹¹ It is estimated that between 40–55% of the variance in ASD is attributed to environmental risk factors.^{18,19} Some of the environmental factors most strongly associated with the risk of ASD include maternal infections during pregnancy, autoimmune issues, foetal exposure to toxins, pollutants and certain types of medications, pregnancy complications, maternal stress, health and nutrition, and advanced paternal age.^{20–22} Regarding the genetic predisposition, there are a number of genetic disorders that are known to be associated with higher rates of ASD, such as Rett Syndrome, Fragile X and Down Syndrome, further illustrating the multiple aetiologies associated with this disorder.²³ Large scale whole genome analyses have identified additional susceptibility genes and processes involved in host defence and immune adaptive mechanisms that can contribute to ASD in the presence of specific environmental factors.^{24–28}

Individuals with ASD have a significantly higher prevalence of comorbid mental and physical health conditions compared to the general population.^{29–33} Such comorbidities

span a whole range of different conditions affecting various systems of the body including immune conditions, gastrointestinal (GI) disorders, metabolic conditions and seizure disorders. Importantly, physical health problems are persistent over the lifespan and are over-represented in very young children, including newborns who are later diagnosed with ASD, as well as in young people and adults with ASD.^{34,35} The concordance of ASD in monozygotic twins is significantly higher in those with a history of early physical conditions.³⁶ Early-life physical health problems and infant dysregulation, for example abnormal crying, feeding and sleeping difficulties, have been proposed as reliable early red flags for ASD screening.³⁷

Premature mortality is estimated to be three to ten times higher for individuals with ASD.^{38–40} Many early deaths are attributed to physical conditions, including seizures, sepsis, cancer as well as immune, respiratory and GI conditions such as constipation, outside of other accidental factors. Post-mortem studies have also revealed an association between ASD and the presence of often undiagnosed physical conditions.^{41,42} As a result of such comorbidities, those diagnosed with ASD also have much higher health care utilisation and associated costs.³³

There is a wealth of scientific data demonstrating the over-representation of various mental and physical health conditions alongside ASD. There is, however, still insufficient recognition amongst healthcare professionals that such symptoms could be related to comorbid physical health conditions rather than being commonly dismissed as “part of autism” or “autistic behaviours”. In this paper, we provide a literature review of the key physical comorbidities identified in people with ASD covering the areas of neuroinflammation and immune dysregulation, GI dysfunction, metabolic abnormalities, as well as seizure disorders such as epilepsy. We also discuss how healthcare professionals, working in partnership with individuals with ASD and their parents/carers, have a duty to be informed about the challenges and considerations in identifying physical comorbidities in this population. Hence, recognising and responding to such additional physical needs will provide equality in their healthcare experiences, and improve their quality of life as well as reducing their morbidity and premature mortality.

Neuroinflammation and Immune Dysregulation in ASD

There is abundant published evidence showing that over half of individuals with ASD present with immune

dysregulation and neuroinflammation.^{43–46} Various clinical trials and experimental animal research have identified abnormal immune function as being central to the pathogenesis of ASD for at least a subset of individuals diagnosed with the condition.^{47,48} The severity of various types of immune alterations has also been found to correlate with the severity of the core features of ASD.^{49–52}

A connection between immune dysfunction and ASD is continued in studies identifying a range of ASD susceptibility genes known to be involved in inflammatory signaling, immune function and infections.^{27,53,54} Genetic associations between ASD and autoimmune disease, such as multiple sclerosis, have also been observed.⁵⁵ Furthermore, several large studies have detailed pro-inflammatory biomarkers indicative of dysfunctional immune responses in mothers and newborns who were later diagnosed with ASD.⁵⁶ In addition, epidemiological studies have consistently shown an association between prenatal infection/immune activation, maternal/infantile atopic diseases, food allergies/intolerances as well as family history of autoimmunity and risk of ASD.^{57–62} Repeated investigations have found chronic inflammatory processes in multiple areas of the brain and cerebrospinal fluid of individuals with ASD, including increased inflammatory cytokine and chemokine production and consistent activation of astrocytes and microglia.^{63–66}

It is of particular interest that large doses of interferon-alpha, a pro-inflammatory cytokine given to humans in cancer treatment, can cause symptoms that can mimic ASD. Symptoms include a decline in speech, executive functioning and cognition as well as motor coordination, anxiety and irritability issues.^{67,68} Animal model studies have similarly shown that exposure to proinflammatory agents can lead to the emergence of ASD-like symptoms.^{69–72} In addition, offspring of animals exposed to immune stressors such as infections or allergies can also develop ASD-like symptoms, including deficits in social interactions, communicative impairments, and repetitive/stereotyped behaviours as well as sleep disturbances and epileptiform activity that closely mirror those observed in ASD.^{73–75}

Autoimmunity in ASD

Autoimmune disorders are characterised by an abnormal immune response to “self”, where “self” tissues are recognised as foreign by the host immune system, leading to a cascade of adverse events and the dysfunction of these tissues or cell types. A number of studies have shown

a high prevalence of autoimmune conditions in families of individuals with ASD compared to the general population. Such autoimmune conditions include coeliac disease, psoriasis, type I diabetes, rheumatoid arthritis, autoimmune thyroid disease and antiphospholipid syndrome.⁷⁶ In addition, mothers of ASD children have been found to have elevated levels of brain-reactive autoantibodies that are passed to their child in utero and react to foetal proteins.⁷⁷ This so-called maternal antibody-related (MAR) autism could potentially equate to around 10% of all cases of autism.⁷⁸

The severity of adaptive functioning and communication impairments in the offspring have been correlated to the levels of maternal autoantibodies.⁷⁹ Animal studies cast further light on such associations, where IgG antibodies derived from mothers of children with ASD were found to cause abnormal brain development and social functioning when transplanted to primate animals.⁸⁰

The presentation and the severity of core autistic symptoms and the presence of various autoantibodies have been linked.^{81,82} Studies have shown that children with ASD and a family history of autoimmunity had significantly higher frequency of systemic serum antinuclear antibodies. These autoantibodies can cause tissue damage via multiple mechanisms, including neurotoxicity.⁸³

Although still the topic of some discussion, research reports have recommended further study on a possible role for PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections) or PANS (Pediatric Acute-onset Neuropsychiatric Syndrome) in relation to ASD.⁸⁴ PANDAS/PANS represent infection-induced autoimmune conditions that disrupt typical neurological functioning. The conditions manifest as rapid onset obsessive compulsive disorder (OCD) and/or motor tics,⁸⁵ alongside other behaviours that potentially overlap with the diagnosis of ASD. There are some important clues about the pathophysiology of PANDAS/PANS pertinent to autoimmunity and ASD. Specifically the infection-triggered autoimmune response and/or molecular mimicry that characterise the conditions, targeting brain structures such as the basal ganglia, provide a template for further investigations.

Autistic Regression and Its Association with Infection, Autoimmunity and Inflammation

Autistic regression is characterized as the emergence of ASD symptoms and functional impairments after an initial

period of normal or typical development. While many children who are later diagnosed with ASD present with developmental delay from birth, an estimated quarter to a third of all cases demonstrate normal development followed by some regression characterised by a loss of previously achieved language and/or other developmental skills.⁸⁶ 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 the emergence of motor impairments are frequently noted around the time of regression. Changes can be seen as abrupt (occurring within days) or progressive, evolving more gradually over a period of several months. There appears to be a strong correlation between autistic regression and poorer long-term outcomes.⁸⁷ While the regression usually occurs between the ages of 12–24 months, several studies have reported unusual patterns of regression. This includes regressions involving severe and/or sudden-onset motor dysfunction, recurring regressions and/or regressions after age three years.^{88,89}

Cases of autistic regression in young children are not typically the subject of detailed investigations, and the precise contributing mechanisms are largely unknown. An emerging body of evidence suggests however, that immune dysregulation and autoimmune phenomena could be one potential pathogenic mechanism in at least a subset of cases.⁸⁸ Cases of autistic regression following viral and bacterial encephalitis have been reported in previously healthy and typically-developing children^{90–93} as well as in adolescents and even adults.^{94–97}

Autistic regression has also been reported in cases following the onset of autoimmune proliferative syndrome, or autoimmune anti-N-methyl-D-aspartate receptor antibodies (NMDAR-Ab) encephalitis.^{98–100} NMDAR-Ab encephalitis is a well-characterised clinical-immunological syndrome caused by an autoimmune reaction to neuronal NMDA receptors. In adults, the initial symptoms are mostly neuropsychiatric in nature, with an often rapid global health deterioration including the occurrence of hypoventilation, catatonia, cerebellar ataxia and loss of consciousness. The symptoms in children are typically less severe and more difficult to recognise. One of the main presenting features of NMDAR-Ab encephalitis in children is loss of language and social skills and reduced interest in surroundings; some of the hallmarks of ASD. 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.^{101,102} All of those features, in varying degrees of severity, are commonly present in idiopathic autism. An awareness of a potentially important role for autoantibodies in some cases of ASD is required by healthcare professionals. Such appreciation should particularly extend to those individuals with ASD who have a familial history of autoimmune-related diseases and/or seizure disorder.

Allergic Diseases in ASD

The manifestations of allergic disease, including IgE and non-IgE mediated reactions, are being increasingly recognised to encompass both behavioural and neurological indicators alongside classical somatic markers.^{103,104} Diagnoses such as anxiety and mood disorders show important relationships with allergic reaction biological markers. Such allergic reactions can contribute to difficulties in focusing, irritability, hyperactivity, daytime fatigue and sleep problems in both young people and adults.¹⁰⁵ Treatment of allergy can also positively impact on behaviour, where symptoms of anxiety and mood disorders for some diminish following allergy treatments.¹⁰⁶

Atopic disease, asthma and food allergies are common in individuals with ASD.¹⁰⁷ The presentation of core ASD symptoms - impaired social communication and repetitive and/or stereotyped behaviours - are seemingly connected to allergic manifestations, alongside other neuropsychiatric symptoms such as anxiety, hyperactivity, and irritability.^{108–111} The assumption is that the pain and discomfort following allergic conditions exacerbate challenging behaviours and cognitive dysfunction in individuals with ASD. In some cases, the treatment of allergies has been reported to result in improvements in challenging behaviours and cognitive function.¹¹² In addition, some findings suggest shared pathological mechanisms,^{113–116} and experimental animal studies have even demonstrated a possibility that allergic neuroimmune activation might underlie some of the symptoms and behavioural abnormalities associated with ASD.¹¹⁷

Imbalances in the hypothalamus-pituitary-adrenal axis (HPA) and the sympathetic axes can result from allergic diseases such as atopic dermatitis and allergic rhinitis. Such an imbalance is thought also to affect cognition and behaviour. Whilst still the topic of investigation, adrenaline release via histamine or direct activation by mast cell involvement are likely involved.¹¹⁸ Given the high prevalence of

allergic diseases, non-IgE mediated hypersensitivity reactions and mast cell over-activation in ASD, as well as confirmed HPA dysfunction with abnormal stress reactivity and sympathetic over-activation, it is possible that, in at least some individuals with ASD, some aberrant behaviours that are frequently characterised as “autistic behaviour” can be related to preventable allergy and intolerance issues.

Allergic and/or non-IgE hypersensitivity should be ruled out when a young person or adult with ASD presents with agitation, irritability, aggression, anxiety, sleep difficulties, lack of concentration, hyperactivity and daytime fatigue.

Gastrointestinal Dysfunction in ASD

GI disorders are significantly overrepresented in ASD compared with the general population.¹¹⁹ Individuals with ASD present with frequent functional issues of diarrhoea, constipation, and gastroesophageal reflux alongside higher rates of inflammatory bowel diseases.¹²⁰ Various other clinical findings appear to be overrepresented in ASD, including increased intestinal permeability, various digestive enzyme deficiencies and bacterial dysbiosis.^{121–123} Children with ASD present with higher rates of lymphoid nodular hyperplasia, esophagitis, gastritis, and duodenitis.^{124,125} The presence of GI dysfunction in children with ASD is, in most cases, not associated with medication or peculiar dietary habits or medication.¹²⁶ Importantly, there is a strong correlation between the presence of GI symptoms and the severity of ASD-related symptoms and behaviours, including irritability, aggression, rigid-compulsive behaviours, anxiety, sensory over-responsivity and dysregulated sleep issues.^{127–129}

Analyses of the GI bacterial composition as well as the identification of bacterial metabolic and biochemical markers in the urine of individuals with ASD have demonstrated the presence of atypical microbiota.^{130,131} Translocation of bacterial species to other parts of the GI tract and indeed, outside of it, has also been described.¹³² This has led to the proposal that treatment aimed at rebalancing the gut flora could alleviate some symptoms associated with ASD. There is some emerging evidence in support of the use of pre- and probiotics for the management of behavioural issues associated with ASD.^{133–135}

There is existing guidance in the peer-reviewed literature recommending that healthcare professionals consider the possibility of behavioural manifestations of GI disorders in individuals with ASD “as those can be atypical and evident only as a change in behaviour, thus presenting

a significant challenge to both parents and healthcare providers”.¹³⁶ Authors explicitly described how, in young people with ASD, faint and anomalous behavioral symptoms should increase suspicion for the existence of constipation. A routine programme of screening, identification and treatment of constipation and its underlying causes is appropriate. Other authors have similarly urged the need for appropriate investigations,¹³⁷ again stressing a possible connection between GI symptoms and behaviour as well as acknowledging that issues such as a limited verbal capacity can affect the quality of care received.

Non-Coeliac Gluten Sensitivity (NCGS) and ASD

Dietary changes, predominantly including the adoption of gluten- and casein-free diets, have been a feature of autism research and practice for many years. Early preliminary research,¹³⁸ published case studies^{139,140} and parental reports of beneficial changes in ASD symptoms following such dietary regimes litter the peer-reviewed literature. Despite no universal effect being reported thus far,¹⁴¹ research continues in this area, specifically concentrating on determining potential non- and best-responders to such nutritional changes.¹⁴²

Debate persists as to the effect and mode of actions of gluten and casein containing foods on individuals with ASD. Insufficiency of numerous digestive enzymes, such as disaccharidases and lactase, has been consistently reported in this population.¹²¹ Preferential screening for coeliac disease has been indicated.¹⁴³ Case reports have noted an improvement in presentation of ASD-related symptoms following a gluten-free and/or casein-free diet in cases of dual ASD and coeliac disease.¹⁴⁴

Alongside examples of clinically-indicated coeliac disease, evidence is emerging for non-coeliac gluten sensitivity (NCGS) in some cases of ASD.^{145–148} While the exact prevalence and clinical manifestations of NCGS in the general population are still the subject of investigation (with continued steps towards definitive description), the existence of NCGS as a new clinical entity has recently been confirmed and classified through large-scale double-blinded studies.¹⁴⁹ Identification of NCGS is currently based on exclusion criteria and following the outcome of a gluten-free diet.

Individuals with ASD and a history of allergy and atopic disease are more likely to suffer from NCGS.¹⁵⁰ Carroccio et al¹⁵¹ observed that mucosal eosinophil

infiltration was a primary histological feature of non-coeliac wheat sensitivity. Such infiltration has been reported in cases of pediatric ASD. Adoption of a gluten-free diet has also been reported to positively affect such clinical findings.^{152,153}

Healthcare professionals need to be familiar with NCGS and its possible appearance in cases of ASD. Those on the autism spectrum displaying symptoms of irritable bowel syndrome or those with potential allergic and other immune-related symptoms may be particular candidates for further screening and inquiry. In this context it is also important to highlight how various neurological dysfunctions can also show a relationship with gluten sensitivity, and can arise independent of noticeable GI symptoms. Familiarity with the various neurological and neuropsychiatric presentations linked to ingestion of foods containing gluten - mood and anxiety disorders, ataxia, migraine, neuropathy and seizure disorders - which may indeed underlie some of the symptoms commonly associated with ASD^{154,155} is an important requirement.

Seizure Disorders and Epilepsy in ASD

The frequency of seizure disorders including epilepsy is notably greater in individuals with ASD compared to the general population. Estimates suggest that around 20% of individuals with ASD will develop epilepsy at some stage in their life¹⁵⁶ with a sizable number also presenting with subclinical epileptiform activity in the absence of a clinical seizure disorder.¹⁵⁷ While an association between the more severe forms of ASD and epilepsy has been known for many years, recent detailed investigations have also shown a high rate of EEG abnormalities and epilepsy risk in individuals with high-functioning ASD.¹⁵⁸ Conversely, the frequency of ASD and related diagnoses is also elevated among individuals with epilepsy compared with the general population.¹⁵⁹

Aside from the significant impact that epilepsy can have on a person's life, it is a leading cause of the elevated premature mortality risk in ASD.³⁹ Accurate and timely diagnosis and treatment of epilepsy is vitally important. Intervention approaches as and when atypical epileptiform activity is present, can lead to a significant abatement of aberrant behaviours and improvements in psychosocial function, alongside decreasing seizure activity.^{160,161} Such a connection implies that some behaviours commonly attributed to ASD may in some cases be due to epileptic activity itself. In addition to clinical seizures, successful treatment of subclinical epileptiform discharges

has also been shown to improve cognitive function and ASD-related symptoms and behaviours.¹⁶² Apart from their possible detrimental effects on cognitive and executive function in individuals with ASD, abnormal isolated epileptiform discharges (IEDs) have been observed to convert to clinical seizures in over 20% of the sufferers in a 2-year follow up study.¹⁶³ Other findings support the diagnostic use of EEG in individuals with ASD.¹⁶⁴

For those individuals who have failed prior psychopharmacology attempts, and those who exhibit unusual and challenging behaviours—for example, sudden and unprovoked outbursts of aggression, irritability, crying, screaming or self-harming, unusual facial and body movements and postures, staring spells, covering of ears—an EEG could be helpful for differentiating between seizures and non-epileptic paroxysmal behaviours.^{165,166}

Metabolic Irregularities, Acquired Mitochondrial Dysfunction and Oxidative Stress in ASD

Children and adults with ASD are at significantly greater risk for weight issues and obesity than the general population.¹⁶⁷ Compared with those presenting with milder impairments, individuals with severe ASD also show an increased likelihood of obesity alongside various other metabolic disorders including hypertension, diabetes and dyslipidemia.^{29,32,168} While the reasons for increased obesity rates in ASD are commonly assumed to be due solely to poor eating habits, the lack of physical activity and/or medication, increased weight gain has been recorded during early infancy¹⁶⁹ pointing to possible involvement of intrinsic biological factors. Such findings complement other studies observing that maternal obesity may be a significant risk factor for offspring ASD.^{170,171} Interestingly, and in common with autism, obesity has been found to be associated with a dysregulated gut microbiota,¹⁷² offering the possibility of a common underlying cause or pathways. Whether maternal obesity or other conditions more likely to appear alongside obesity (eg hypertension, diabetes, dyslipidemia, alteration of gut microbiota) are causative of such enhanced risk for offspring ASD remains to be elucidated.

Consistent scientific findings point to elevated levels of oxidative stress and perturbed methylation processes, atypical energy metabolism and mitochondrial dysfunction and disruption in sulphur and amino acid biochemistry in ASD compared to the general population.^{173,174} There is

also strong evidence that such processes may have an intricate, and likely pathogenic, connection in at least a subset of ASD.¹⁷⁵

While cellular energy production in the brain has been reported as impaired in individuals with ASD, inflated levels of markers of oxidative stress alongside reductions in glutathione and other important cellular antioxidants have been reported in other body regions and in immune cells.¹⁷⁶ Atypical detoxification systems present in cases of ASD have also been associated with the severity of cognitive and social impairments.¹⁷⁷ Atypical mitochondrial energy metabolism - elevated blood, urine and cerebrospinal fluid levels of pyruvate, lactate and alanine alongside serum carnitine insufficiency - have been reported in cases of ASD.¹⁷⁸ In the majority of cases this abnormal energy metabolism cannot be linked to an identifiable genetic cause or another primary inborn error of metabolism.¹⁷⁹ The metabolic and chemical changes observed in individuals with ASD are instead suggestive of a dynamic dysfunction process secondary to outside stressors.¹⁸⁰ Some authors have proposed that the mitochondrial and metabolic anomalies appearing alongside ASD ensue following immune dysfunction¹⁸¹ or an abnormal microbiome.¹⁸² Inadequate mitochondrial energy production could both result from and add to cellular oxidative stress and chronic inflammation in individuals with ASD. Reactive oxygen species are damaging to cells and organs. Inflated levels of oxidative stress are suspected in various other inflammatory and autoimmune diseases. Chronic inflammation as an important function in various metabolic disorders manifesting behavioural and cognitive features is also likely relevant to ASD.¹⁸³

Studies investigating metabolic markers in the context of ASD have also revealed a variety of important findings. In one study an inborn error of metabolism was detected in 7% of children.¹⁸⁴ Cerebral folate deficiency, together with folate receptors autoantibodies, have also been reported to play a pathological role in cases of ASD.¹⁸⁵

Healthcare professionals should have awareness of and screen for metabolic and/or mitochondrial dysfunction as these physical comorbidities can potentially contribute to ASD severity.

Motor Dysfunction, Connective Tissue Disturbance and Movement Disorders in ASD

Motor difficulties are an important facet of many cases of ASD. Some of the earliest descriptions of ASD included

discussion of motor deficits¹⁶⁸ although formal diagnostic criteria have so far not included this important area of functioning. Various different types of motor dysfunction and movement disorders have been noted in ASD.¹⁸⁷ Such observations cover both fine and gross motor skills. Despite the lack of formal acceptance of such deficits, motor skill dysfunction shows some important correlations with other core ASD features.¹⁸⁸ Ehlers-Danlos Syndrome (EDS), a disorder of the connective tissue characterised by joint hypermobility and a wide range of articular and non-articular manifestations including GI symptoms, has also been reported alongside ASD.¹⁸⁹

Sensory Dysfunction and Abnormal Pain Reactivity in ASD

Another important feature of ASD is sensory processing and dysfunction. Covering all of the primary senses - auditory, visual, tactile, olfactory and gustatory input - there is a wealth of scientific literature noting differences in the sensation and/or processing of sensory data in ASD.¹⁹⁰ Sensory dysfunctions and abnormal processing of pain also seemingly underlie some of the more challenging behaviours associated with ASD^{191,192} and are a facet of the current diagnostic criteria for ASD. Various studies have highlighted a strong connection between sensory dysfunction and the presentation of other core ASD features.

Identifying Physical Comorbidities in ASD – Challenges and Considerations

In this paper, we have highlighted a number of physical comorbidities that are associated with ASD (see [Figure 1](#)). Recognising the physical comorbidities in individuals with ASD is challenging. A primary reason is that ASD is not traditionally seen as being related to any physical ailments but solely the result of behavioural and neuropsychiatric dysfunction. We argue that the main barrier to better awareness and recognition is this paradigm within which many healthcare professionals operate. Another reason is that the expression of physical comorbidities in ASD is sometimes atypical.

Various factors need to be considered to enable the accurate recognition of physical health comorbidities in individuals with ASD. Challenging behaviours such as aggression or self-injurious behaviour (SIB) in individuals with ASD may be the dominant or exclusive symptom of a hidden physical condition, which can be acute or chronic

Figure 1 Physical health comorbidities associated with ASD.

as well as progressive or static. Individuals with ASD often respond to pain with challenging behaviours. For example common target body areas of SIB include biting of the hands (especially in the area between thumb and index), the head (frontal, temporal and back of the head) and the jaw areas.

Symptoms such as grimacing, appetite disturbances, insomnia and strange postures are not core features of ASD. A considerable volume of scientific evidence points to the possibility of an underlying physical cause to such behaviours. To avert diagnostic overshadowing, screening for physical conditions should be initiated when such behaviours are observed.

A functional analysis of challenging behaviours is warranted to identify the root cause(s) of such behaviours. These could be purely behavioural (ie attention seeking, access to tangibles, escape, sensory) and/or be related to physical health. The sudden onset of challenging behaviour, often described as “out of the blue” by parents and carers, more specifically suggests an underlying physical cause and warrants further evaluation. For example, a sudden occurrence of compulsive behaviour and tics might be associated with

infection and/or autoimmune conditions; abnormal, out of context laughter and sudden onset of aggressive behaviour could be related to gut dysbiosis or seizures.

Parents and carers typically provide accurate and valuable information about the symptoms and behavioural changes observed in their children. However, they may be unaware of the possible causes of these changes, especially when they have been advised that these are ‘simply what autism is’.

Individuals with ASD who are perceiving pain and/or discomfort may be unable to report either the pain itself or the physical location within their body. Hence, the use of visual aids and augmentative communication tools may be useful. Equally the use of a non-communicative pain checklist can be helpful.¹⁹³ In order to tackle morbidity and preventable death in individuals with ASD it is of utmost importance to provide regular physical health checks and to maintain high level of clinical suspicion towards physical health problems in ASD.

Conclusion

Physical health comorbidities occur significantly more frequently in individuals with ASD than in the wider general

population. Such comorbidities include neuroinflammation and immune dysregulation, GI dysfunction, metabolic abnormalities, acquired mitochondrial dysfunction and oxidative stress as well as seizure disorders such as epilepsy. Some of the physical symptoms presented by those with ASD have been erroneously attributed to the core behavioural and neurological features of ASD. Impairments in social interaction and communication are, by their definition, central symptoms of ASD. They obscure the recognition of underlying physical comorbidities by clinicians. It is of utmost importance to raise awareness among healthcare professionals and bridge the gap between physical health and the implication of ASD as a whole body disorder. Leaving these physical conditions undiagnosed and untreated clearly results in health inequalities. They can also significantly decrease a person's quality of life potentially leading to morbidity and/or premature mortality.

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