Medical Comorbidities in Autism Spectrum Disorders

A Primer for Health Care Professionals and Policy Makers

Second Edition: July 2014

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To protect the privacy of individuals, all names in the case examples have been changed.

Executive Summary

Autism spectrum disorder (ASD) is a complex and highly heterogeneous neurodevelopmental condition. While ASD is currently diagnosed on the basis of the presence and severity of core abnormalities in social communication and repetitive behaviours, many common medical conditions are now known to be significantly more prevalent in people with ASD compared to the general population. Premature mortality is also significantly increased in ASD. Yet, according to widespread reports and published case studies, there have been many cases of symptoms of medical conditions, sometimes severe, being attributed without investigation to 'behaviours', 'mental health issues' or just ASD itself.

Difficulties with communication can represent a significant barrier to accessing appropriate health care for individuals with ASD. These problems can be compounded if a parent or a carer is not aware that symptoms should be reported as important, especially if these symptoms have been dismissed any time in the past. 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 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, symptomatology, behaviours and other possible consequences of medical comorbidities in ASD, thus enabling improved patient care, enhanced quality of life for people with ASD, reduced dependency and decreased long-term costs.

Introduction

Many children and adults diagnosed with an ASD have comorbid health problems. Recent large-scale studies, including a detailed assessment conducted by the US Centers for Disease Control and Prevention (CDC), have confirmed that several medical conditions are significantly over-represented in people with ASD compared to the general population and other developmental conditions prevalence estimates.

Individuals with ASD have much higher than expected rates of various medical conditions studied, including: ear and respiratory infections, food allergies, allergic rhinitis, atopic dermatitis, type I diabetes, asthma, gastrointestinal (GI) problems, sleep disorders, schizophrenia, headaches, migraines, seizures and muscular dystrophy (Chen, 2013; Gurney, 2006; Isaksen et al., 2012; Kohane et al., 2012; Mazurek et al., 2012; Schieve et al., 2012).

> "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."
>
> *Isaksen et al., 2012. 'Children with autism spectrum disorders: The importance of medical investigations.'*

A recent large-scale study that examined health records of 2.5 million individuals found significantly higher than normal rates of nearly all major medical and psychiatric disorders in adults with ASD, including GI disorders, epilepsy, dyslipidemia, vision and hearing impairments, hypertension, autoimmune conditions, asthma, allergies, and others, extending across all age groups (Croen et al., 2014). This study confirms findings of previous ones that observed that, without intervention, there is a significantly enhanced risk for developing many medical conditions in adults with ASD (Tyler et al., 2011). Adults with developmental disabilities are also at much higher risk for osteoporosis and show severe degrees of bone demineralisation (Jaffe et al., 2001; Jaffe and Timell, 2003). The results of these studies indicate that the **biologic makeup of individuals with ASD contributes to some of the illnesses**. Alongside an increasingly aging population with ASD, the impact of other age-related health comorbidities on quality of life and risk of early mortality remains to be seen (Perkins et al., 2012).

Early mortality is significantly increased in ASD, with death rates being three to ten times higher than the general population (Bilder et al., 2013; 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; Shavelle et al., 2001) alongside accidental causes of death resulting from risky and dangerous behaviour.

***"Adults with ASD have a significant burden of major psychiatric and medical conditions. Their underlying impairments in social communication and increased sensory sensitivities 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."* (Croen et al., 2014)**

"Treatment of comorbid medical conditions may result in a substantial improvement of quality of life both of the child and their parents. What investigations should be implemented can vary both within the autism spectrum and individually."

Isaksen et al., 2012 'Children with autism spectrum disorders: The importance of medical investigations.'

While persons with ASD have higher rates of medical comorbidity and early mortality, as well as much higher health care utilisation and costs, they also consistently experience barriers in accessing appropriate medical care (Barrett et al., 2012; Gurney, 2006; Liptak et al., 2006; Tregnago, 2012). Combined with the behavioural manifestations of ASD and difficulties with communication, these medical conditions generate challenges to clinicians regarding recognising, assessing, and managing the illness (Olivie, 2012; Venkat et al., 2012). One study found that nearly a third of adults presenting with high functioning autism reported that they had not received appropriate medical care for physical health problems (Nicolaidis et al., 2013). It is feared that **suboptimal medical care is even more likely for those severely affected by autism** and less able to communicate with clinicians and carers.

In a 2014 survey conducted by Treating Autism of families with ASD (n=304) only 22% of respondents reported that "the person with ASD had a thorough investigation of his/her symptoms from an NHS practitioner". When asked what type of symptoms NHS professionals had dismissed as the result of ASD, answers included frequent vomiting, severe constipation, hyperactivity, diarrhoea, screaming, self-injury, sleeping only a few hours a night, seizure-like behaviours, aggressive outbursts, failure to grow, contorting/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 and paediatricians, while 51% and 46% respectively were "unsatisfied"; 80% of respondents had sought private medical help for their children with ASD (Treating Autism survey, 2014).

In order to ensure that patients with ASD are not disenfranchised from the healthcare system **it is of paramount importance that health professionals do not dismiss unusual symptoms and presentation of medical illness as being behavioural or 'a part of autism'**. Pain and physical problems in individuals with ASD—especially for approximately 40% of the population with severe communication difficulties or intellectual disability—frequently present in atypical ways and therefore are often erroneously dismissed as behavioural or mental health problems. In addition to reports by carers, published case studies provide examples of such 'diagnostic overshadowing' and illustrate how easily those unusual 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 can be argued that dismissal of atypical manifestation of pain and physical issues as 'autism behaviours' represents outright discrimination towards patients, 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'*, i.e. disability (Equality Act 2010).

***"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)**

In this regard, there is no evidence supporting the attribution of behaviours such as head banging, night waking, aggression and posturing directly to the pathophysiology of autism. In fact, there is substantial evidence to the contrary, as reflected in a consensus report published in the journal of the American Academy of Pediatrics (AAP), which states that: **"Care providers should be aware that problem behavior in patients with ASDs may be the primary or sole symptom of the underlying medical condition, including some gastrointestinal disorders."** (Buie et al., 2010a).

The AAP, in their widely distributed Autism A.L.A.R.M. (2004), encourages clinicians to listen to parents, because they *"generally DO give accurate and quality information"*. However, it is also important to recognise that parents or carers may face communication barriers with their ASD child and that this problem is exacerbated if they 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 manageable or treatable with appropriate health care.

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, the shifting research field indicates that some of the symptoms and behaviours that frequently occur in autism have been erroneously assumed to be a result of autism itself, or are vaguely labelled as a mental health problem, including anxiety, 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 so-called 'autistic 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; Quek et al., 2012; Sukhodolsky et al., 2008). Challenging behaviours in particular are frequent and debilitating among persons with ASD; a recent study found higher than expected prevalence of aggressive behaviours, with parents reporting that 68% of their ASD children had demonstrated aggression to a caregiver and 49% to non-caregivers (Kanne and Mazurek, 2011). The costs, both human (Hodgetts et al., 2013) and monetary (Buescher et al., 2014; Cidav et al., 2012; Lavelle et al., 2014) reflected by these statistics are incalculable, especially given the ever-increasing autism rates (Centers for Disease Control and Prevention, 2012; 2014; Ouellette-Kuntz et al., 2014; Zahorodny et al., 2012).

"This recent and rapid increase in ASD prevalence underscores the importance of continuing surveillance to monitor trends in the population and the need to continue expanding research into risk factors, etiology, and effective interventions."
(Centers for Disease Control and Prevention, 2014)

Current state of knowledge

Current neurological, immunological, metabolic, endocrinological and epidemiological research is at the leading edge of a paradigm shift in our understanding of ASD. Studies published in the peer-reviewed domain over the last few years confirm many earlier findings of **widespread biomedical abnormalities** as being present in cases of autism. While ASD has been commonly assumed to be 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. The core deficits in communication, social interaction, restrictive/stereotypic behaviours, and other commonly seen behaviours noted in ASD, are reasonably explained as **surface manifestations of a variety of systemic and complex biological processes.**

Accumulating scientific evidence challenges the previously-held belief that autism is an in-born and unchangeable condition, as numerous studies now confirm that normally developing children can suddenly lose their developmental milestones and previously acquired language and social skills, and regress into autism. The reasons why this happens are largely unknown, as unfortunately regressions are rarely a subject of detailed clinical investigations, such as the ones discussed below. Those children who lose their previously acquired skills and regress into autism comprise over 30% of all autism cases, and there seems to be a clear association between regression and negative long-term functional outcomes (Barger et al., 2012; Goin-Kochel et al., 2014). Furthermore, there are an increasing number of reports of unusual patterns of regression—including repeated regressions, regressions involving losses of gross motor function, and/or regressions after age three years (Weismann et al., 2008).

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, always in the direction of the occiput. This would make a loud clunking noise. At the same time he developed a penchant for jumping from ever increasing heights. On examination he had bilateral purulent ear effusions. He 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.**

In some cases there are very defined circumstances—illuminated by detailed clinical investigations—around the reasons for such regression. These cases include the onset of Anti-N-Methyl-D-Aspartate (NMDA) receptor 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; Scott et al., 2013). Other circumstances involve encephalopathic illness of viral origin. While acute illnesses caused by a herpes virus, especially cytomegalovirus, are the most frequently reported ones (DeLong et al., 1981; Ghaziuddin et al., 2002; Gillberg, 1986; Libbey et al., 2005; Stubbs, 1978), 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 (Baldaçara et al., 2011; Mankoski 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).

Preliminary reports of prolonged steroid therapy improving long term outcomes in children with idiopathic autism lend weight to theories that inflammatory and/or immune-related processes play a causative role in autistic regression (Duffy et al., 2014). **Unfortunately for patients and their families, in the vast majority of cases the circumstances of autistic regression, such as loss of speech and sudden behavioural regression, do not normally trigger medical inquiry.**

Some children on the autism spectrum present with decreasing symptoms, or even complete recovery from ASD following intensive interventions of various kinds (Anderson et al., 2013; Barger et al., 2012; Ekinci et al. 2012; Eriksson et al., 2012; Fein et al., 2013; Mukaddes et al., 2014; Orinstein et al., 2014; Pellicano, 2012). 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."* (Ozonoff, 2013). Such research also adds weight to the suggestion that autism is a plural, and a highly heterogeneous, condition. Despite some commonalities in behavioural presentation, ASD may be more aptly referred to as 'the autisms' (Whitehouse et al., 2013) with likely **different biological underpinnings**. This variability of underlying pathological mechanisms and the existence of different subtypes in autism are critical factors that must be taken into consideration when interpreting biomedical treatment trials in autism: it is highly likely that many such trials fail to reach statistical significance simply because of the failure to distinguish biological subtypes and to identify best responders.

While further studies are under way to elucidate the exact reasons why some typical children may descend into autism, or why some children lose their autism following intervention, it is now well established that **specific medical problems are associated with the severity of the condition**. Successfully addressing these comorbidities can lead to significant improvement in overall functioning for individual patients.

***"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).**

Some of the biomedical abnormalities found to date in ASD include, but are not confined to: neuroinflammation and immune dysregulation, abnormal gut flora, autonomic dysfunction, oxidative

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.**

stress and mitochondrial dysfunction. All of these abnormalities can have pathological consequences and clear negative impact on behaviour and neurological functioning both in child- and adulthood.

Neuroinflammation and immune dysregulation in ASD

A large proportion of individuals with ASD show signs of persistent neuroinflammation, altered inflammatory responses, and immune abnormalities. There is now considerable evidence of abnormal immune function being one of the key features in at least a subset of autism and this potentially plays a role in the pathogenesis of the disorder. Both the population-wide studies as well as experimental animal research point to immune-related pathways being directly involved in the development of ASD symptoms and manifestations (see section 'Immune system in ASD: translational research and clinical evidence').

Postmortem and in vivo investigations have found **chronic inflammatory processes** such as microglial activation in multiple areas of the brain and the central nervous system (CNS) (Chez et al., 2007; Edmonson et al., 2014; Li et al., 2009; Morgan et al., 2012; Suzuki et al., 2013; Tetreault et al., 2012; Vargas et al., 2005; Wei et al., 2011; Young et al., 2011). Impairments of microglial function could offer substantial explanation of mechanisms of possible environmental injury in ASD, as microglia are known to react to environmental changes and influence the developing brain and its synaptic plasticity through epigenetic mechanisms.

These findings of chronic neuroimmune activation in the brain and CNS are accompanied by serum findings, all pointing to **widespread and chronic dysregulation of immune mechanisms**. Individuals with ASD display excessive and skewed cytokine responses, abnormal T cell reactivity, modified NK function, abnormal myeloid dendritic and mast cell activation (see 'Allergic disorders in ASD'), white cell abnormalities and increased autoantibody production (Abdallah et al., 2012; Afaf El-Ansary and Al-Ayadhi, 2012; Breece et al., 2013; Enstrom et al., 2009; Ginsberg et al., 2012; Hsiao, 2013b -review; Kameno et al., 2013; Masi et al., 2014; Molloy et al., 2006; Naik et al., 2011; Rodrigues et al., 2014; Suzuki et al., 2011).

A possible causal relationship between impaired immune response and metabolic and mitochondrial dysfunction in ASD has recently come to light (Napoli et al., 2014) (also see section 'Metabolic abnormalities, acquired mitochondrial dysfunction and oxidative stress in ASD'). In addition, correlation has been found between levels of immune dysfunction—in particular levels of circulating cytotoxic T-cells—and abnormal neural connectivity and cognitive and executive dysfunction in ASD (Al-Ayadhi and Mostafa, 2013; Ashwood et al., 2011; Han, 2013). Similarly, the levels of macrophage migration inhibitory factor (MIF), a cytokine that is implicated in the pathogenesis of sepsis and inflammatory and autoimmune diseases, are also increased in ASD and correlate to severity of symptoms (Grigorenko et al., 2008).
These observations resemble findings in other inflammatory and immune-mediated disease states, in which elevations in levels of cytokines or autoantibodies to 'self' tissues are associated with the pathogenesis of neuroinflammation, neurotoxicity and neuronal injury, and subsequent behavioural and cognitive impairments, for example multiple sclerosis or HIV-induced neurological dysfunction.

> "Recognition from health care professionals that comorbid medical conditions such as GI disturbances, sleep disorders, and epilepsy were real issues that affect children with ASD was sorely needed."
>
> *Lajonchere et al., 2012 'Leadership in Health Care, Research, and Quality Improvement for Children and Adolescents With Autism Spectrum Disorders: Autism Treatment Network and Autism Intervention Research Network on Physical Health'*

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

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; Chen et al., 2014; Chez and Guido-Estrada, 2010; Chez et al., 2012; Duffy et al., 2014; Gupta et al., 1996; Kraneveld et al., 2014; Lv et al., 2013; Matarazzo, 2002; Ramirez et al., 2013; Sandler et al., 2000; Sharma et al., 2012; Stubbs et al., 1980). 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 (Gupta, 2000; Plioplys, 1998). Future research should aim to distinguish such individuals, in order to best predict potential responders to such treatments.

"The elevated mortality risk associated with ASD in the study cohort appeared related to the presence of comorbid medical conditions and intellectual disability rather than ASD itself suggesting the importance of coordinated medical care for this high risk sub-population of individuals with ASD."

Bilder et al., 2012 'Excess Mortality and Causes of Death in Autism Spectrum Disorders'

Allergic disorders in ASD: effects of allergies on behaviours and neurodevelopment

Allergic diseases are significantly more prevalent in ASD and appear to influence the development or severity of symptoms and problematic behaviours in at least a subset of affected individuals. Various allergic manifestations, including asthma, nasal allergies, atopic diseases (IgE-mediated), and food intolerances are now known to be common in ASD and to extend across all age groups (Chen et al., 2013; Croen et al., 2014; Kohane et al., 2012; Schieve et al., 2012). Furthermore, there appears to be a **positive association between the frequency and severity of allergic manifestations and severity of autism**, where allergic diseases have been observed to be linked to both the core symptoms of autism—impaired social interaction and communication and repetitive and stereotyped patterns of behaviours—as well as 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).

***"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)**

It has been demonstrated that a challenge with nasal allergens results in an increase in autism symptoms in over half of children studied (Boris and Goldblatt, 2004) while treatment of allergies often results in improvement in negative and challenging behaviours and better overall functioning (Chen et al., 2013; 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; Mostafa and Al-ayadhi, 2013; Theoharides, 2013; Tsai et al., 2014). Additional evidence that **allergic neuroimmune activation may underlie core autism symptoms and behavioural abnormalities in some cases** has been provided by experimental animal studies (de Theije et al., 2013; Tonelli et al., 2009).

An increasing body of evidence points to a connection between the presence of allergic diseases, including food allergy, and behaviour and neurological development (Chang et al., 2013; Khandaker et al., 2013; Meldrum et al., 2012). Both IgE and non-IgE mediated allergic reactions are recognised causative factors of anxiety and mood disorders. Such allergic reactions contribute to difficulty focusing, irritability, tics, hyperactivity, daytime fatigue and sleep problems in both children and adults (Dahl et al., 1995; Shyu et al., 2012). Children with allergies suffering from learning disabilities, hyperactivity, fatigue, incoordination and irritability who are treated for their allergies show marked improvement in ability to learn and to perform intelligence tests, as well as a reduction in hyperactivity and incoordination (Chen et al., 2012; Millman et al., 1976; Price et al., 1990). Similarly, a large population-based study recently found considerable reductions in anxiety, aberrant mood and behaviours in adults who receive allergy treatments compared to those left untreated (Goodwin et al., 2012).

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 ENT, and subsequently underwent a tonsillectomy. Within two weeks mood improved, obstinance ceased and his school grades returned to normal.**

According to the report by Neuroallergy Committee of the American College of Allergy:

***"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).**

Allergic diseases like atopic dermatitis and allergic rhinitis are characterised by an imbalance of the hypothalamus-pituitary-adrenal axis (HPA) and the sympathetic axis, which in turn can influence behaviour and cognition. These effects are most likely mediated through effects of histamine on adrenaline release but also via direct activation of HPA by pro-inflammatory molecules released by mast cells, which have long been implicated in stress-induced immune responses (Kalogeromitros et al., 2007; Liezmann et al., 2011; Scaccianoce et al., 2000).

Given the high prevalence of allergic diseases and non-IgE mediated hypersensitivity reactions and mast cell over-activation in ASD, as well as confirmed HPA and sympathetic over-activation (see section 'Dysfunction of the Autonomic Nervous System and HPA axis in ASD'), it seems likely that many aberrant behaviours that are frequently characterized as 'autism', and possibly some of the core symptoms of ASD in a subset of individuals, are being caused or exacerbated by potentially treatable and preventable allergic reactions.

Health professionals should be aware that when a child or adult with autism presents with 'autistic irritability' or increased aggressiveness, anxiety, inability to fall or stay asleep, inability to concentrate, hyperactivity and daytime fatigue, the possibility of allergic and non-IgE hypersensitive conditions should be considered. Treatment of allergies can result in improvement in negative and challenging behaviours, and better overall functioning.

Non-coeliac gluten sensitivity and ASD

Interventions involving the use of diets devoid of gluten (a protein found in wheat and other cereal grains) and/or casein (the protein found in mammalian milk and dairy sources) have some research history in relation to autism (Whiteley et al., 2013). The most recent Cochrane systematic review of gluten- and casein-free (GFCF) diets for ASD, published in 2008, recommended that large scale, good quality randomised controlled trials are still needed. From the trial evidence available at the time it concluded that "*the diet poses no disbenefit or harm*" and it identified positive effects of the diet relating to improvement in overall autistic traits, social isolation, and overall ability to communicate and interact (Millward et al., 2008). Research continues in this area (Buie, 2013; Whiteley et al., 2010) with a particular focus on identifying potential best- and non-responders to such dietary intervention (Pedersen et al., 2013; Whiteley et al., 2014).

Debate also continues regarding the nature of the effect of gluten on some of the behavioural presentations of autism as well as its particular mode of action. Screening for gluten-related conditions such as coeliac disease in cases of autism has been indicated (Barcia et al., 2008) and case reports have noted abatement of autistic presentation where a gluten-free and/or casein-free diet is installed in cases of dual autism and coeliac disease diagnoses (Genuis et al., 2010; Herbert and Buckley 2013; Whiteley et al., 2014). **Deficiency of various digestive enzymes**, such as lactase and disaccharidases, has 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 at al., 2011; Williams et al., 2011; 2012). In a 2014 survey conducted by Treating 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" (Treating Autism, 2014).

CASE EXAMPLE 4 **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 continuously slapping the screen. On examination he had marked tonsillar enlargement with marked erythema, and reactive anterior cervical chain lymphadenpathy. Bloods 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.**

"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 'Autism spectrum disorders and allergy: Observation from a pediatric allergy/immunology clinic'

***"The findings indicate that the observed anti-gliadin immune response in patients with autism is likely to involve a mechanism that is distinct from celiac disease"* (Lau et al., 2013)**

Recent large-scale double-blinded studies have confirmed the existence of **non-coeliac gluten sensitivity (NCGS) as a new clinical entity**, and classification has been introduced for gluten-related non-coeliac food sensitivities. Questions are still being asked in relation to the prevalence and clinical manifestations of NCGS, and steps are being taken towards proper characterisation, including clinical markers of the condition. At the present time the diagnosis of NCGS is based on exclusion criteria and an elimination diet of gluten-containing foods followed by an open challenge to evaluate whether patient health improves with the elimination or reduction of gluten from the diet (Dodou et al., 2014; Sapone et al., 2012).

Patients with a history of allergies and atopic diseases are more likely to suffer from non-coeliac food sensitivity (Carroccio et al., 2012; Massari et al., 2011). Since children with ASD are more likely to suffer from atopy and allergies, **possible NCGS or wheat sensitivity in those children needs to be considered**, especially when irritable bowel syndrome symptoms are present. It should be noted that Carrocio and colleagues (2013) found that the main histological characteristic of non-coeliac wheat sensitivity was mucosal eosinophil infiltration. Histological findings of prominent mucosal eosinophil infiltration have been observed in a high percentage of children with autism, and appear to be significantly lower in children following a gluten-free diet (Ashwood et al., 2003; Chen et al., 2010).

***"Lactase deficiency not associated with intestinal inflammation or injury is common in autistic children and may contribute to abdominal discomfort, pain and observed aberrant behavior"* (Kushak at al., 2011).**

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. (2013) 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 ASD** (Lau et al., 2013; de Magistris 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 relevance to autism could be findings by Caio and colleagues, who observed normalisation of levels of those same antibodies and mast cell reactivity in NCGS patients who followed a gluten-free diet for six months: "*Anti-gliadin antibodies [AGA] of the IgG class disappear in patients with non-celiac gluten sensitivity reflecting a strict compliance to the gluten-free diet and a good clinical response to gluten withdrawal*" (Ciao et al., 2014). Furthermore, the possible relationship of gluten sensitivity and coeliac serology in some cases of epilepsy could be of relevance to autism, discussed below. (see section 'Seizures Disorders in ASD').

***"In children with unclear neurologic manifestations with probable autoimmune etiology, anti-TG2 autoantibody titers should be determined considering the possibility of gluten sensitivity. Gluten-free diet remains the only effective treatment reported to date and, therefore, should be recommended to all patients with gluten sensitivity despite the type of manifestations."* (Jorge et al., 2014)**

CASE EXAMPLE 5 **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 antifungals 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.**

It is important in this context to point out that various types of neurological dysfunction are well known manifestations of gluten sensitivity in humans, and can occur even in the absence of gut involvement. **Health professionals should be aware of the possibility of NCGS being present in some patients with ASD, especially in those presenting with atopic diseases, migraines, mood and anxiety disorders**. Clinicians are advised to become familiar with the common neurological presentations, such as seizure disorders, ataxia, neuropathy, migraine, and mood and anxiety disorders, as well as the means of diagnosis of this disease (Hadjivassiliou, 2014; Peters et al., 2014).

Autoimmunity in ASD

The connection between autoimmune disorders in mothers and ASD in their offspring is being established, with a number of studies demonstrating a high prevalence of family history of autoimmune conditions compared to general population. Maternal conditions such as diabetes, rheumatoid arthritis, lupus, psoriasis, celiac disease, antiphospholipid syndrome and autoimmune thyroid disease are significantly associated with a greater risk of ASD in the offspring (Abisror et al., 2013; Atladóttir et al., 2009; McDougle and Carlezon, 2013; Mostafa et al., 2014; Sweeten et al., 2003) and a recent large-scale study reported that autoimmune disorders are found 20%-30% more often in adult females with ASD than controls (Croen et al., 2014). In addition, brain-reactive antibodies are increased in the mothers of ASD children. It has been suggested that **maternal antibody-related (MAR) autism could represent over 20 percent of all idiopathic autism** (Brimberg et al., 2013; Xu et al., 2013).

A correlation has been found between levels of maternal antibodies and severity of communication impairments and adaptive functioning (Piras et al., 2014). Such connections are further explicated by an experimental study in which autism-related IgG antibodies from mothers of children with autism altered normal brain growth and social behaviour in primates (Bauman et al., 2014). Maternal autoantibodies associated with autism may impact brain development leading to abnormal enlargement (Nordahl et al., 2013).

In the light of published reports of regression into autism in children with acquired NMDA-encephalitis, as discussed above, consideration should be given to the potential of lupus-related and similar autoantibodies playing a causative role in some cases of idiopathic autism (Vinet et al., 2014). Autoantibodies to glutamate receptors and calcium channels should be given particular attention, since glutamate is a major neurotransmitter in the brain involved in synaptic plasticity and emotional responses. The neurotoxic action of these maternal antibodies and cytokines has been shown to cause abnormal brain development and behaviours in offspring in animal experiments (Faust et al,. 2010; Lee et al., 2009; Meszaros et al., 2012).

***"Antibrain antibodies do play an important pathoplastic role in autism. Prenatal and/or postnatal exposure to these antibodies enhances autism severity by impairing cognitive processes and adaptive functioning, boosting motor stereotypies, altering the sleep/wake cycle, delaying or halting neurodevelopment especially in reference to verbal and non-verbal language. Our results, along with previous studies performed 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)**

Finally, an **association between serum levels of various autoantibodies in ASD individuals and severity of their autistic symptoms** has been repeatedly observed (Chen et al., 2013; Frye et al., 2012; Mostafa and Al-Ayadhi, 2012). A recent study found that ASD children with a family history of autoimmunity had significantly higher frequency of

CASE EXAMPLE 6 **Sally is an 11-year old girl with late regressive autism. She presented with a six-month history of worsening self-harm, head-banging, obsessions and episodic aggression against others. Previously Sally was placid with episodic obsessional behaviours. On examination Sally held her head frequently and disliked bright lights. When asked where it hurts Sally localised to the top of her head. Apart from some mild right iliac fossa tenderness there was little else to find. Bloods showed ASOT of 800 (nr >200), ESR of 12 and platelets of 350. Rheumatoid Factor was markedly elevated at 104 (nr >14). She was commenced on co-amoxiclav and prednisolone and referred to Paediatric Neurology and Rheumatology. Within three days her symptoms had reduced substantially. There was no self-harm, no aggression and Sally returned to her placid self. Speech was significantly improved, and Sally was able to express widespread joint pain.**

"Developing effective treatments and improving care for individuals with ASDs throughout the life span remain urgent priorities."

James M. Perrin, MD, Harvard Medical School, President-elect of the American Academy of Pediatrics

systemic serum anti-nuclear antibodies, whose potential to contribute to tissue damage by multiple mechanisms, including neurotoxicity, is well documented (Mostafa et al., 2014). As discussed above, preliminary reports of steroid therapy improving long term outcomes in children with regressive autism lend further weight to theories that autoimmune processes could play a pathological role in some forms of idiopathic autism (Duffy et al., 2014).

These findings have led many researchers and clinicians to suggest that autoimmune mechanisms could be a causative or contributing factor in at least a subset of individuals with ASD, and multiple studies are underway to further illuminate autoimmune pathological mechanisms in autism with the view of developing targeted tests and treatments. **Health professionals, especially immunologists, neurologists and others who receive referrals should be aware of the potential pathological role autoantibodies may play in some patients with ASD, especially those with a family history of autoimmune disease or seizure disorder.**

***"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)**

Immune system in ASD: translational research and clinical evidence

Growing evidence suggests that the prenatal environment, and particularly the maternal immune environment, plays a critical role in some cases of ASD. In addition to maternal antibodies, as discussed above, core autism symptoms and neuroimmune pathologies can also be induced in offspring by maternal exposure to infection, inflammatory immune mediators and specific types of medications. These outcomes have been deduced from maternal clinical histories as well as observed in animal experiments. Numerous rodent studies show that exposure to inflammatory agents causes gender-specific neurological, behavioural and cognitive disturbances as well as long-lasting immune abnormalities in young animals (Dada et al., 2014; Elmer et al., 2014; Foley et al., 2014; Gibney and Drexhage, 2013; Onore et al., 2014), as well as disturbances in the composition of their microbiota and levels of serotonin and other neurotransmitters in their GI system (de Theije et al., 2014). Maternal immune activation in **primate models of autism** produces symptoms that overlap with the core diagnostic domains of ASD, including **repetitive behaviours and impaired communication and social interactions**, and the timing of these behavioural alterations corresponds to emergence of autism symptoms in human toddlers (Bauman et al., 2013; Martin et al., 2008).

"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

CASE EXAMPLE 7 **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 distended abdomen, alternating diarrhoea and constipation and marked malodour. He became prone to ear infections, had chronic dermatitis, head banging every 2 hours, cracked lips, allergy shiners.**

Jameel received a diagnosis of autism at age 2 years and 7 months. At presentation Jameel was underweight, distressed, uncooperative and unhappy.A number of laboratory tests were undertaken and several issues were identified: elevated total IgE and eosinophil count (allergy against foods and inhalants identified), low Natural Killer Cell Count, markedly elevated ASLO titer, deficiencies in iron, vitamin D, Omega 3, together with raised proprionic acid, hippuric acid and 4-hydroxyphenyacetic acid.

Successful treatment consisted of dietary exclusion, good environmental hygiene, correction of deficiencies, and combination antimicrobials for intestinal bacterial overgrowth. Over three months sleep normalised, vocalisation, eye contact and understanding improved. Head banging stopped. Bowels improved.

abnormalities in major psychiatric illnesses." **(Meyer, 2014)**

Correcting immune abnormalities in post-exposure animals with immune-modulatory treatments results in normalisation of their immune function, and more importantly, improvements in cognitive function and **reversal of autism-related symptoms and behaviours** (Kipnis et al., 2004; Hsiao et al., 2012; Naviaux et al., 2014).

Activation of the immune system is known to lead to structural and functional changes in both central and autonomic nervous systems and to impact behaviour. Prolonged peripheral inflammation, even when subclinical, causes **'sickness behaviours', characterized by reduced affection 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).

Similarly, the presentation of patients suffering from chronic inflammatory, infectious or autoimmune disease, or undergoing cytokine therapy, demonstrates that immune dysregulation can impact behaviour, mood, personality and cognitive function in humans. Addressing CNS or peripheral infections, for example in the gastrointestinal system or sinuses; calming autoimmune reactions; or discontinuing therapy with inflammation-inducing agents often lead to **reversal and normalisation of behaviours and restoration of normal brain function** (Dantzer and Kelley, 2007; Kraneveld et al., 2014; Myint et al., 2009; Siegel and Zalcman, 2008; Wolters et al., 1994).

A link between immune dysfunction and ASD is further exemplified by multi-genome analysis studies that found links between genes that are involved in inflammatory signalling, which predispose individuals to aberrant immune response to infections and the risk of developing autism (Al-Hakbany et al., 2014; Herbert et al., 2006; Grigorenko et al., 2008; Saxena et al., 2012; Ziats and Rennert, 2011). Genomic associations between ASD and some autoimmune diseases like multiple sclerosis have been discovered (Jung et al., 2011), and several studies involving large European birth cohorts have found perturbed immune responses and pro-inflammatory biomarkers in mothers and their newborns who are later diagnosed with ASD (Abdallah et al., 2012; 2014; Brown et al., 2013; Zerbo et al., 2013). Furthermore, the causal links between prenatal rubella (Chess, 1971) and cytomegalovirus infections have been repeatedly observed (Ivarsson et al., 1990; Markowitz, 1983; Sakamoto et al., 2014; Stubbs et al., 1980; Sweeten et al., 2014). There are indications that placental function is one of the factors determining negative neurodevelopmental outcome in congenital infections (Kitajima et al., 2012; Walker et al., 2013b).

In this context it must be mentioned that the most rigorous and largest population-based twin studies of autism done to date have found that *"susceptibility to ASD has moderate genetic heritability and a substantial shared twin environmental component"* and *"although genetic factors also play an important role, they are of substantially lower magnitude than estimates from prior twin studies of autism"* (Hallmayer et al., 2011; Sandin et al., 2014).

Genetic variability likely predisposes for increased susceptibility to environmental challenges, as current evidence, albeit limited, of genetic risk for ASD lies mainly in immune-related genes (see above). The **importance of environmental factors for autism risk** is further illustrated by findings of impaired methylation and epigenetic dysregulation of autism-associated genes (Wong et al., 2014; Zhu et al., 2014). Furthermore, the largest genome-wide association studies performed on more than 5000 individuals in total, have failed to detect any specific gene association with any consistency across the studies (Anney et al., 2012; Liu et al., 2013; Pinto et al., 2010; Wang et al., 2009; Weiss et al., 2009). These studies identify a small number of ASD individuals with novel genetic changes called Copy Number Variation or CNV. However, the effects of genetic variants on the risk for ASD "are modest" as Pinto et al. 2010 state, "*the population attributable risk ... is estimated to be 3.3%*". This implies that 96.7% of ASD cannot be attributed to these genetic changes.

"Perpetuating the myth of autism as a primarily genetic disorder is a disservice to those who might benefit from treatment and diverts attention from nongenetic causes."

Prof Richard Deth, Northeastern University, Boston

Gastrointestinal comorbidities and abnormal bacterial flora in ASD

Gastrointestinal (GI) problems are significantly over-represented in ASD and can often be related to problem behaviours, sensory overresponsitivity, dysregulated sleep, rigid–compulsive behaviours, aggression, anxiety and irritability (Chaidez et al., 2013; Chandler et al., 2013; Mazefski et al., 2013; Mazurek et al., 2012; Peters et al., 2013; Schurman et al., 2012). The largest ever meta-analysis published in the April 2014 edition of *Pediatrics* confirmed a strong link between GI disorders and autism (McElhanon et al., 2014), and the results from a large-scale population-based study conducted by the US CDC showed that children with ASD, in addition to having many other unmet health needs, experience far more gastrointestinal problems than children with other developmental delays, those with learning disability, or typical controls (Schieve et al., 2012). GI disorders are also significantly higher in adults with ASD than normal, as confirmed by the largest study of its kind that examined medical records of more than 2.5 million adults (Croen et al., 2014).

In recent years there has been an increased recognition of gastrointestinal comorbidities—**both functional bowel problems and pathological findings**—among individuals with autism, including increased intestinal permeability, diarrhoea, constipation, gastroesophageal reflux, digestive enzyme deficiency and bacterial dysbiosis (de Magistris et al., 2010; 2013; Horvath et al., 1999; Kushak et al., 2011; Ming et al., 2012; Persico and Napolioni, 2012; Wang et al., 2012; Williams et al., 2011). In children with ASD undergoing endoscopy, high rates of lymphoid nodular hyperplasia, oesophagitis, gastritis, duodenitis, and colitis have been described, and preliminary evidence suggests that some features may be unique to **gastrointestinal inflammation specific to autism** (Horvath et al., 1999; Torrente et al., 2004; Walker et al., 2013).

CASE EXAMPLE 8 **David is a 34-year old male with mild to moderate autism. He presented with a two-month history of unexplained aggressive outbursts. Despite reasonable communication skills he could not explain the outbursts of rage. Examination was unremarkable. Routine investigations revealed H.Pylori. His rage episodes resolved after eradication therapy and one month on a proton pump inhibitor.**

"Unrecognized gastrointestinal disorders, especially reflux esophagitis and disaccharide malabsorption, may contribute to the behavioral problems of the non-verbal autistic patients." **(Horvath et al., 1999)**

The **strong correlation of gastrointestinal symptoms with severity of autism** indicates that children more severely affected by autism are likely to have severe gastrointestinal symptoms (Adams et al., 2011; Gorrindo et al., 2012; Wang et al., 2011). Recent research has also confirmed that, contrary to commonly-held beliefs, presence of gastrointestinal dysfunction in children with autism is **not associated with distinct dietary habits** or medication status, and **parental reporting of any GI dysfunction in their children is highly concordant with later clinical diagnosis** of that dysfunction (Gorrindo et al., 2012).

A consensus paper published in the journal of the American Academy of Pediatrics recommends that health care providers should be alerted to the behavioural manifestations of gastrointestinal disorders in patients with ASD, "*as those can be atypical and evident only as a change in behavior, 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 might indicate the presence of constipation and that screening, identification, and treatment through a deliberate approach for underlying causes of constipation is appropriate.

In individuals with autism, atypical presentations of common gastrointestinal problems can include emergence or intensifying of seemingly non-related 'autistic' behaviours 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 *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 pathophysiology 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).

Analyses of the bacterial flora composition of individuals with ASD have frequently revealed the presence of abnormal bacteria that are absent from healthy controls, as well as translocation of bacterial species to parts of gastrointestinal system that are not host to those bacteria in healthy individuals (De Angelis et al., 2013; Ekiel et al., 2010; Finegold et al., 2002; 2010; Parracho et al., 2005; Williams et al., 2012). The systematic review papers by Cao and colleagues (2013) and Hsiao (2014) provide excellent overviews of the collected research findings in this area up to October 2013 and March 2014 respectively, although they do not include several important replicative studies including that by Wang et al. (2013) on the presence of Sutterella species in cases of ASD.

"Our results suggest that clinicians should screen for constipation and diarrhea or underwear staining symptoms in children with ASD who have prominent rigid–compulsive symptoms." **(Peters et al., 2013)**

Metabolic/biochemical changes found in the urine of individuals with ASD further confirm the gut microbiota abnormalities revealed by stool and ileal tissue investigations (Ming et al., 2012; Yap et al., 2010). Endotoxemia has been observed in patients with ASD, and the levels of **bacterial toxins in the blood** have been found to correlate to severity of autism symptoms (Emanuele et al., 2010). This is believed to result from both the increased presence of pathogenic bacteria and the increased intestinal permeability seen in ASD. A small treatment trial of oral vancomycin noted a decrease in autism-related behaviours following a course of this antibiotic (Sandler et al., 2000). This observation, which has since been confirmed by clinical reports, case studies and controlled animal experiments, points further to a possible correlation between levels of pathogenic bacteria and severity of autistic symptoms (Hsiao et al., 2013; Ramirez et al., 2013).

> "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 if they have adverse gastrointestinal effects."
>
> *Buie et al., 2010 'Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report.'*

"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 discussed above, pain and sickness have profound influences on mood, cognition, and behaviour, including sociability and communication. Equally, chronic inflammation and infections of the GI tract are associated with increased circulatory levels of pro-inflammatory cytokines with direct effect on

CASE EXAMPLE 9 **Luke is a 5-year old boy with regressive autism. With intensive intervention he made good progress, but marked anxiety in social situations remained. Parents complained that he suffered uncontrolled terror when he even went near a busy play park. Parents had resorted to taking him very early in the morning. On examination he had a pulse of 100 BPM, with further increase upon questioning/challenging. He was commenced on 20mgs of propranolol in the morning and 10mgs in the afternoon. Immediate resolution of social anxiety ensued. Within one week Luke was playing for 30 minutes in a busy park. He has made further advances in development since.**

"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, overestimated."

Hallmayer et al., 2011 'Genetic heritability and shared environmental factors among twin pairs with autism'

behaviour, including anxiety, motivation, socialisation, avoidance of novel situations, and adherence to routine and repetitive actions. Pathogens or mediators derived from the immune system interact with endocrine and peripheral neural pathways, such as the intestinal enteric nervous system and the autonomic nervous system, and consequently affect brain function (Cryan and Dinan, 2012; Goehler et al., 2005; Goehler and Gaykema, 2009; Sharkey and Kroese, 2000). In animal models of autism, animals exposed early in life to bacterial toxins develop autistic traits (Baharnoori et al., 2012; de Theije et al., 2013a; 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).

***"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)**

Subclinical gastrointestinal infections, such as Small Intestinal Bacterial Overgrowth (SIBO) are known to affect normal brain development and functioning and induce anxiety and aberrant behaviours. These effects are mediated mainly through dysregulation of the hypothalamic–pituitary–adrenal axis, the autonomic nervous system/vagus nerve, and serotonin signalling, all of which are abnormal in autism (Diaz Heijtz et al., 2011; Foster and McVey Neufeld, 2013) (also see section 'Autonomic Dysfunction in Autism').

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

Metabolic abnormalities, acquired mitochondrial dysfunction and oxidative stress in ASD

There is now substantial evidence that impaired energy metabolism and mitochondrial dysfunction, including brain energy metabolism, perturbation in sulfur and amino acid metabolism, high levels of oxidative stress and impaired methylation processes are more common in persons affected by autism than other groups, and could play a major pathological role in at least a subset of the disorder (Goh et al., 2014; Weissman et al., 2008). While cellular energy production in the brain is impaired in autism, elevations in oxidative stress as well as significantly reduced levels of glutathione and other cellular antioxidants have been found in many other areas of the body, including the immune cells such as leukocytes (Chauhan et al., 2012; Ghezzo et al., 2013; Gu et al., 2013; Legido et al., 2013; Muratore et al., 2013; Napoli et al., 2014; Rose et al., 2012; 2014). Levels of oxidative stress and mitochondrial dysfunction correlated strongly with autism severity in one study, suggesting increased vulnerability to oxidative stress in those with more severe impairments (Essa at al., 2013). Correlation between severity of social and cognitive impairments and impaired detoxification mechanisms in ASD is further

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 ESR 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.**

illustrated by preliminary findings of increased levels of several toxic metals and other environmental toxicants, as well as decreased activity of glutathione-S-transferase and lowered concentrations of vitamin E in children with ASD compared to typical controls (Adams, et al., 2013; Alabdali et al., 2014; Rossignol et al., 2014b; Yorbik et al., 2010).

***"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)**

A substantial percentage of patients 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; Frye et al., 2013a; Oliveira et al., 2005). In the majority of cases this abnormal energy metabolism **cannot be linked to genetic causes** (Hadjixenofontos et al., 2013) or another primary inborn error of metabolism. However it is known that in many cases of metabolic diseases, such as urea cycle disorders, inborn errors of biopterin or purine metabolism, autistic features may be a leading, or sometimes the only visible clinical feature of the underlying disease (Mayatepek, 2010). Abnormal cholesterol synthesis can also have autism as a presenting feature, and in some cases improvements in behavioural symptoms are noted following normalisation of cholesterol metabolism (Calvo et al., 2014; Diaz-Stransky et al., 2012).

Furthermore, in a recent study that screened 187 children with ASD, metabolic biomarkers were discovered in 7%, and for those 13 patients, treatment with biotin supplementation or institution of a ketogenic diet resulted in mild to significant clinical improvement in autistic features (Spilioti et al., 2013). In addition, cerebral folate deficiency, as well as autoantibodies to folate receptors, are suspected to play a pathological role in some cases of idiopathic autism because of their negative effects on cerebral folate metabolism and well-known involvement in other neurodevelopmental syndromes. Both of these conditions are often responsive to folinic acid therapy (Frye et al., 2012; Hyland et al., 2010; Moretti et al., 2005; Rameakers and Quadros, 2010; Ramaekers et al., 2012) (also see section 'Autoimmunity in ASD'). Positive reports on the use of exclusion diets in autism, as discussed in previous chapters, raise the possibility that dairy-free diets may in some instances decrease folate autoantibodies levels (Ramaekers et al., 2008).

The metabolic and chemical changes observed in ASD brains are suggestive of a **dynamic disease process secondary to outside stressors** (Corrigan et al., 2013; Tang et al., 2013). It has therefore been suggested that in ASD, metabolic and mitochondrial abnormalities could occur as a downstream consequence of immune dysfunction (Palmieri and Persico, 2010; Rose et al., 2014; Rossignol and Frye, 2011; 2014), or abnormal or harmful microbiome (Ming et al., 2012; Persico and Napolioni, 2013; Wang et al., 2012).

Insufficient mitochondrial energy production could result from and contribute to cellular oxidative stress and chronic inflammation in ASD. Reactive oxygen species are destructive to cells and organs, and elevated oxidative stress has been implicated in autoimmune, inflammatory, cardiovascular and neurodegenerative diseases, and cancer. Of likely relevance to autism is also the discovery of a complex role of chronic inflammation in metabolic disorders, with effects on cognition and behaviours (Lasselin et al., 2014).

In this context the most striking findings were recently revealed by Naviaux and colleagues (2014). In their experimental study maternal immune activation was used to induce an animal model of autism. Behavioural abnormalities were accompanied by immune and mitochondrial dysfunction in affected animals, as well as motor abnormalities, mirroring impairments found in people with ASD. The researchers then targeted ATP mitokines, a signalling system in the body that is made by distressed mitochondria and that is critical to innate immunity. Weekly administration of antipurinergic agent suramin corrected 16 multisystem abnormalities in the animals, including mitochondrial and other metabolic dysfunction, neuronal loss, disruption of brain synapse structure and signalling, **following which there was a normalisation of social behaviour and motor coordination** (Naviaux et al., 2014). Human trials with suramin are currently under way.

Raising antioxidant levels and/or metabolic

precursors with nutraceuticals such as fatty acids and other ways of supporting mitochondrial function have been proposed as treatment avenues to address biomedical imbalances in ASD, and help reduce negative behaviours, such as hyperactivity (Ghezzo et al., 2013). Small clinical trials of antioxidants such as ubiquinol (CoQ10); carnosine and N-acetyl-l-cysteine (NAC); mitochondrial agents such as carnitine; and metabolic precursors such as methylcobalamin and folinic acid have shown promising preliminary results (Bertoglio et al., 2010; Chez et al., 2002; Fahmy et al., 2013; Ghanizadeh and Derakhshan, 2012; Gvozdjáková et al., 2014; James et al., 2009; Rossignol and Frye, 2011). NAC in particular seems to be a promising avenue for reducing irritability (Hardan et al., 2012; Ghanizadeh and Moghimi-Sarani, 2013) or self-injurious behaviour (Marler et al., 2014) in some individuals with ASD. Tetrahydrobiopterin (BH4) has also shown very encouraging results, with statistically significant results noted across domains such as improvements in social awareness, autism mannerisms, hyperactivity, and inappropriate speech (Klaiman et al., 2013; Frye et al., 2013b). In addition to improving some of the aberrant behaviours associated with autism, treatments such as l-carnitine 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).

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

Dysfunction of the Autonomic Nervous System and HPA axis in ASD

Dysfunction of the autonomic nervous system (ANS) in autism has been gaining increasing attention in recent years. **Elevated sympathetic and lowered parasympathetic activity** is frequently present in children and adults with ASD whether or not they have more obvious outward symptoms or signs of autonomic abnormalities, with several studies reporting alterations in heart rate and heart rate variability, mean arterial and diastolic blood pressure, atypical pupillary light reflex (Anderson et al., 2013b; Cheshire, 2012; Daluwatte et al., 2013; Ming et al., 2005; Patriquin et al., 2011) and atypical autonomic response to anxiety (Kushki et al., 2013). Raised levels of plasma noradrenaline have also been found, indicative of a chronic state of hyperactivity of the sympathetic nervous system (Lake et el., 1997). Furthermore, findings of lower baseline respiratory sinus arrhythmia have been reported, suggesting a reduced vagal modulation in children with ASD (Bal et al., 2010).

Widespread abnormalities in the functioning of the hypothalamic–pituitary–adrenal (HPA) axis, another system closely involved in the stress responses, have also been observed. 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, have been found in individuals with ASD compared to controls (Corbett et al., 2010; Curin et al., 2003; Iwata et al., 2011; Spratt et al., 2012).

Immune-related factors such as chronic inflammation and heightened allergic reactivity, or factors related to gastrointestinal dysbiosis and microbial translocation in ASD, as discussed before, offer biologically plausible explanations for observed dysregulation of the HPA.

Autonomic and HPA dysfunction are additional neurobiological factors capable of influencing behavioural symptoms of ASD. Given that autonomic signals are essential to emotional processing, it has been suggested that the observed autonomic abnormalities in ASD may contribute to socio-emotional deficits (Eilam-Stock et al., 2014).

Targeting autonomic dysfunction may therefore offer a possible treatment avenue for some of the debilitating symptoms that are frequently present in ASD, such as heightened anxiety and the lack of emotional regulation—including impulsiveness, aggression, and irritability—as well as improving cognitive and verbal functioning (Beversdorf et al., 2011; Bodner et al., 2012; Haspel, 1995; Ming et al., 2008; Murphy, 2000; Narayanan et al., 2010; Ratey et al., 1987; Zamzow et al., 2014).

Seizure disorders in ASD

The prevalence of seizure disorders is significantly higher in people with ASD. The latest figures report the average prevalence of epilepsy in children with autism at approximately 12%, climbing to 26% by adolescence and adulthood (Parmeggiani et al., 2010; Viscidi et al., 2013). Furthermore, subclinical epileptiform activity has been found in a majority of individuals with ASD, even in the absence of clinical seizure disorder (Isaksen et al., 2012; Lewine et al., 1999; Muñoz-Yunta et al., 2008).

Epilepsy is a major contributing factor to the elevated mortality risk seen in ASD, making detection and treatment of this medical comorbidity of utmost importance (Mouridsen et al., 2011, Woolfenden et al., 2012). When epileptiform activity is present, therapeutic strategies aimed at its control can sometimes lead to a significant improvement in language and autistic behaviours, in addition to reducing seizure activity (García-Peñas, 2005; Lewine et al., 1999; Muñoz-Yunta et al., 2008).

***"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).**

Viewing the data from a slightly different stance, the prevalence of ASD and other neurobehavioural abnormalities is significantly higher among patients with epilepsy than in the general population, pointing to shared pathophysiological mechanisms (Helmstaedter et al., 2014; Lin, 2013), such as autoimmune or brain inflammatory mechanism, both of which are implicated in the pathology of autism (Choi and Koh, 2008; Ong et al., 2014; Suleiman et al., 2013; Vincent et al., 2010). Notably, in the maternal infection animal model of autism, emergence of both epilepsy and autism-related symptoms can be prevented by blocking major inflammatory mediators (Sankar et al., 2014).

> "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."
>
> *Lajonchere et al. 2012 'Leadership in Health Care, Research, and Quality Improvement for Children and Adolescents With Autism Spectrum Disorders: Autism Treatment Network and Autism Intervention Research Network on Physical Health'*

***"Epilepsy and autoimmune disease frequently co-occur; 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 some preliminary evidence that the ketogenic diet, which has been widely and successfully used for controlling or ameliorating a broad spectrum of seizure types, also has a potential for ameliorating symptoms of autism in some patients (Evangeliou et al., 2003; Herbert and Buckley, 2013; Spilioti et al., 2013).

Further to this evidence, studies have shown an association between Coeliac Disease (CD)—even in the absence of gastrointestinal symptoms—and epilepsy and cerebral calcifications, as well as positive responses to dietary changes in those patients (Hijaz et al., 2013; Johnson et al., 2013). Since positive coeliac serology has been found in many ASD patients with normal gut mucosa (see section 'Non-coeliac gluten sensitivity and ASD') **investigations into CD, non-coeliac gluten sensitivity, and epilepsy—even in the absence of typical gastrointestinal symptoms or frank seizures—could potentially yield good results for the ASD patient.**

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.**

Approaching comorbidity in the ASD patient: Medical Considerations

Investigating, identifying, and treating any of the many conditions a patient with ASD might be suffering from carries a multitude of challenges. Communicating pain and any other symptoms that may be processed atypically, the level of baseline agitation, the lack of a coherent history, the complexity of disease processes that may be subclinical, and other factors can all contribute to a challenging assessment. In all likelihood, such difficulties underlie at least some of the substantial morbidity and mortality rates in ASD that are consistently reported, and clinicians need to take the steps required to address these challenges. The increasing number of clinical reports and case studies pointing to the positive outcomes of appropriate investigations and treatments offer even more reason to surmount these difficulties.

The following points need to be taken into account to enable accurate diagnosis:

- Problem behaviour in patients 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 not part of the diagnostic criteria of autism. As evidenced by current research and accumulating clinical experience, these and other symptoms and behaviours must not be automatically attributed to either mental health or behavioural problems, or as being inherent to ASD or some preconceived facet of that diagnosis. There is a substantial body of evidence that these behaviours can have physical origins and to prevent diagnostic overshadowing, organic explanations should be sought.
- Parents and carers generally do give accurate and quality information about symptoms or behaviour change; however, parents and carers 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 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.

Premature attribution of physical health issues to the autism phenotype and the consequences thereof, require that all of those with a vested interest in the health of individuals with ASD—professionals, parents, and carers—understand the following checklist, meant to improve recognition of common health problems in ASD:

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 behaviour: finger tapping on throat
- Sensory hyper-responsitivity: 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, wincing, tics
- Self-injurious behaviour: biting, hitting/slapping face, head-banging, unexplained increase in self-injury
- Constant eating/drinking/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
- Seizure Disorder (including subclinical crisis)
- Toothache
- Soft or hard stool constipation (underlying cause will be relevant)
- Sore Throat
- Reflux
- Oesophagitis
- Gastritis
- Colitis
- Small Intestinal Bacterial overgrowth
- Allergy Disorder (including Non-IgE mediated disorders and food intolerances)

(Breau et al., 2002; 2009; Buie et al., 2010; Goldson and Bauman, 2007; Jones et al., 2007; Lea et al., 2012; Munoz-Yunta et al., 2008; Nader et al., 2004; Smith et al., 2012; Tracy and Wallace, 2001; Tudor et al., 2014; Venkat et al., 2012)

Conclusion

Medical comorbidities are much more prevalent in people with ASD than in the general population. Such comorbidities can also be more difficult to recognise. The failure to identify medical conditions is due in part to communication impairments and sometimes ambiguous symptomatology, but widespread underdiagnosis and barriers to accessing appropriate health care for people with ASD are also the result of commonly held beliefs that aberrant behaviours and symptoms are 'just a part of autism'. Leaving these pathologies untreated clearly results in health inequalities and constitutes a gross injustice to the individual.

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 also shows that increased severity of many of these conditions correlates with increased severity of symptoms of 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.

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 stereotypies. 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.

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"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."

Lajonchere et al,. 2012 'Leadership in Health Care, Research, and Quality Improvement for Children and Adolescents With Autism Spectrum Disorders: Autism Treatment Network and Autism Intervention Research Network on Physical Health'

"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.'

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