Medical Comorbidities in Autism Spectrum Disorders

A Primer for Health Care Professionals and Policy Makers

Prepared by:
- Treating Autism
- Autism Treatment Trust

March 2013
Introduction

Many children and adults with a diagnosis of autism spectrum disorder (ASD) have comorbid health problems. Recent large-scale studies have confirmed that several medical conditions are significantly more prevalent in people with autism compared to the typical population. A detailed assessment conducted by the US Centers for Disease Control and Prevention demonstrated that children with autism had much higher than expected rates of all of the medical conditions studied, including: eczema, allergies, asthma, ear and respiratory infections, gastrointestinal problems, severe headaches, migraines, and seizures (Kohane et al., 2012).

Further studies from the US, Europe and Asia that carried out detailed clinical investigations confirmed that medical comorbidities were highly prevalent in children and adolescents diagnosed with ASD. Abnormal clinical findings were common and additional investigations revealed a high prevalence of medical disorders or manifestations, making it clear that "an appropriately extensive medical assessment is essential in all cases" (Isaksen et al., 2012; Mazurek et al., 2012; Memari et al., 2012; Kose et al., 2013).

Mortality is significantly increased in autism, with death rates being three to ten times higher than the general population (Bilder et al., 2012; Woolfenden et al., 2012). These deaths tend to be the result of medical comorbidities, such as epilepsy, gastrointestinal conditions and respiratory disorders (Shavelle et al., 2001; Pickett et al., 2006; Gillberg et al., 2010; Bilder et al., 2012; Woolfenden et al., 2012). One study found that deaths from gastrointestinal and respiratory disorders were 40.8 and 24.5 times higher, respectively, in moderately to severely affected patients versus typical peers (Shavelle et al., 2001). Another study that looked at the general health of adults with autism found that without intervention, those patients appear to be at significant risk for developing diabetes, coronary heart disease, and cancer (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).

Over time, anecdotal reports and opinions on what constitutes ‘autism behaviours’ have been adopted as unofficial criteria in the assessment of autistic patients; however, there is no evidence supporting the attribution of behaviours such as head banging, night waking, aggression and posturing to the pathophysiology of autism. In fact, there is substantial evidence to the contrary, as reflected in the consensus report from the American Association 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., 2010).

"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.”


"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.’

"Comorbid conditions may be markers for underlying pathophysiology and request a more varied treatment approach.”


2001; Pickett et al., 2006; Gilberg et al., 2010; Bilder et al., 2012; Woolfenden et al., 2012. One study found that deaths from gastrointestinal and respiratory disorders were 40.8 and 24.5 times higher, respectively, in moderately to severely affected patients versus typical peers (Shavelle et al., 2001). Another study that looked at the general health of adults with autism found that without intervention, those patients appear to be at significant risk for developing diabetes, coronary heart disease, and cancer (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).

Over time, anecdotal reports and opinions on what constitutes ‘autism behaviours’ have been adopted as unofficial criteria in the assessment of autistic patients; however, there is no evidence supporting the attribution of behaviours such as head banging, night waking, aggression and posturing to the pathophysiology of autism. In fact, there is substantial evidence to the contrary, as reflected in the consensus report from the American Association 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., 2010). Behaviours in the ASD population are often physical in origin, identifiable through investigation, and treatable or manageable through appropriate medical care.

The AAP in their widely distributed Autism A.L.A.M. (2004) encourages clinicians to listen to parents, because they “generally DO give accurate and quality information”. However, like clinicians who are working
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.


Current state of knowledge

Current neurological, immunological, metabolic, endocrinological, and immunological research is at the leading edge of a paradigm shift in our understanding of ASD. Studies published in the last 12 months confirm many earlier findings of widespread biomedical abnormalities in autism. While autism has been commonly assumed to be a neurodevelopmental and behavioural disorder, and kept within the boundaries of psychiatry and neurology, it is now increasingly recognised as a whole-body disorder, with the core deficits in communication, social interaction, restrictive/stereotypic behaviours, and other commonly seen behaviours that have been attributed to ASD, being surface manifestations of a systemic and complex disease process.

Scientific evidence is accumulating that challenges the previously held belief that autism is an in-born and unchangeable condition: numerous studies now confirm that a significant percentage of previously typically-developing children regress into autism, and also that some children present with decreasing symptoms, or even complete recovery from autism or "optimal outcome" (Fein et al., 2013) following intensive intervention (Barger et al., 2012; Ekinci et al., 2012; Eriksson et al., 2012; Pellicano, 2012). Fein et al's study in particular challenges the assumption that ASD is static and lifelong, and provides strong "evidence that recovering from autism is indeed possible and opens up the possibility of improvement, even without optimal normalization." (Ozonoff, 2013).

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

"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 stress and mitochondrial dysfunction—all of which could have pathological consequences and clear negative impact on behavior and neurological functioning.

Neuroinflammation and immune dysregulation in ASD

There is firm evidence of immune dysfunction in individuals with autism. Results of numerous studies point to abnormal immune function, including on-going neuroinflammatory response. Several postmortem and in vivo investigations found chronic inflammatory processes in multiple areas of the brain and multiple studies have found a correlation between levels of immune dysfunction and severity of autistic symptoms (Vargas et al., 2006; Chez et al., 2007; Li et al., 2008; Morgan et al., 2010; Wei et al., 2011; Young et al., 2011; Suzuki et al., 2013). These observations resemble findings in other inflammatory and autoimmune disease states, in which elevations in levels of cytokines or autoantibodies 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.

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 same time he developed a ‘fondness’ for jumping from higher and higher height. 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.

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.
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 and Goldblatt, 2004) while treatment of allergies often results in improvement in behaviours such as anxiety, hyperactivity, and irritability, commonly attributed to ‘being autistic’ (Jyonouchi, 2010; Schieve et al., 2012; Chen et al., 2013).

Both IgE and non-IgE mediated allergic reactions are increasingly recognized causative factors of anxiety and mood disorders. As well, these allergic reactions contribute to difficulty focusing, irritability, tics, daytime fatigue and sleep problems in both children and adults.

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, reduction of hyperactivity and incoordination, and ability to perform intelligence tests (Randolph, 1947; Milman et al., 1976; Price et al., 1980; Chen et al., 2012). The characteristic symptoms of allergic disorders may include bronchial asthma, allergic rhinitis, and atopic dermatitis, all of which may cause difficulty falling asleep as well as night waking due to difficult breathing, itching and scratching. These sleep disturbances lead to daytime inattention, irritability, and hyperactivity (Dahl et al., 1995; Shyu et al., 2012).

Similarly, a large population-based study recently found that the presence of anxiety, aberrant mood and behaviours is considerably reduced in adults who receive allergy treatments compared to those left untreated (Goodwin et al., 2012).

According to a report by the 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).

It is now known that allergic diseases like atopic dermatitis and allergic rhinitis are characterised by an imbalance of the hypothalamic-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 and also via direct activation of HPA by pro-inflammatory molecules released by mast cells, which have long been implicated in stress-induced immune responses (Scaccianoce et al., 2000; Kalogeromitros et al., 2007; Liezmann et al., 2011).

Mastocytosis or mast cell activation syndrome is a spectrum of rare diseases characterized by increased number of activated mast cells in many body organs. Children who are affected by this disorder appear to have autism at a rate tenfold higher than that of the general population children (Angelidou et al., 2011). It has been proposed that excessive activation of mast cells could be the central pathogenic mechanism in at least some types of idiopathic autism. This is currently being investigated by Tufts University researchers, with preliminary treatment trials of mast cell blocking agents yielding promising results (Theoharides et al., 2012a; Theoharides et al., 2012b).

Given the high prevalence of allergic diseases and non-IgE mediated hypersensitivity reactions and mast cell over-activation in autism, as well as confirmed HPA and sympathetic over-activation (see following section), it seems likely that many aberrant behaviours that are frequently characterized as ‘autism’ 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 anxiety, inability to fall or stay asleep, inability to concentrate, hyperactivity and daytime fatigue, the possibility of allergic and hypersensitive conditions should be considered (Jyonouchi, 2010; Goodwin et al., 2012; Theoharides et al., 2012b).

Non-celiac food sensitivity and ASD
Recent large-scale double-blind studies have confirmed the existence of non-celiac wheat sensitivity as a new clinical entity. Patients with a history of allergies and atopic diseases are more likely to suffer from non-celiac food sensitivity (Massar et al., 2011; Carroccio et al., 2012). Since children with autism are almost twice as likely as controls to suffer from atopy and allergies, possible wheat sensitivity in those children needs to be considered, especially when intractable bowel syndrome symptoms are present (see following section) (Menchetti et al., 1995; Sandler et al., 2000; Schieve et al., 2012). A joint clinical trial currently being undertaken by Massachusetts General Hospital and Second University of Naples is focusing on identifying a clinical diagnostic biomarker for non-celiac gluten sensitivity. It should be noted that Carroccio and colleagues (2013) found that the main histological characteristic of non-celiac 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 have been found to be significantly lower in children following a gluten-free diet (Ashwood et al., 2003; Chen et al., 2010). The most recent Cochrane systematic review of gluten- and casein-free diets for autistic spectrum disorder, published in 2009, recommended that large scale, good quality randomised controlled trials are needed.

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 on the background of long-standing constipation. GP had referred to paediatrician, who referred to a paediatric gastroenterologist, who referred to a neurologist. He was commenced on carbamazepine for mood-stabilisation. At consultation he was agitated, preferred to sit, but frequently stood straight, paced over the reception area. The chest examination suggested a tight 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 proton pump inhibitor (omeprazole) of azithromycin resolved the consolidation, and his self-harm and destructive behaviour also resolved. Edward had not localised to the pain source nor had he developed pyrexia.

CASE EXAMPLE 3
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 proton pump inhibitor (omeprazole) 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.
however from the existing trial evidence it concluded that “the diet poses no disbenefit or harm”, and it identified positive effects of the this diet relating to improving in overall autistics, social isolation, and overall ability to communicate and interact (Millward et al., 2008). A more recent review of the literature on the benefits of a gluten free diet in autism found that “although not wholly affirmative, the majority of published studies indicate statistically significant positive changes to symptom presentation following dietary intervention” (Whiteley et al., 2012).

**Autoimmunity in ASD**

The connection between autism and autoimmune disorders is gaining increasing support with a number of studies demonstrating a high incidence of autoimmune conditions in autism and an association between serum levels of various autoantibodies and severity of autistic symptoms (Mostafa and Al-Ayadhi, 2011; Fye et al., 2012; Mostafa and Al-Ayadhi, 2012; Chen et al., 2013). Autoantibodies to folate receptors for example are suspected to play a pathological role in some forms of idiopathic autism because of their negative effects on cerebral folate metabolism and well-known involvement in other neurodevelopmental syndromes (Hylden et al., 2010; Ramaekers et al., 2012).

Similarly, the patient suffering from chronic inflammatory or autoimmune disease, or undergoing cytokine therapy, demonstrates that

**Immune system in ASD: translational research and clinical evidence**

Autism-related symptoms and behaviours can be induced in offspring by maternal exposure to infection and maternal immune mediators. These outcomes have been observed in both animal experiments and maternal clinical histories. Animal models show clear connections between anxiety, abnormal social behaviours and levels of proinflammatory cytokines. Correcting immune abnormalities in perinatal experiment animals with immune-modulatory treatments results in normalisation of immune function, and more importantly, improvements in cognitive function and complete and lasting reversal of abnormal autism-related behaviours (Kipnis et al., 2004; Hisao et al., 2012).

Activation of the immune system is known to lead to functional changes in the central and autonomic nervous system and to impact behaviour. Prolonged peripheral inflammation, even when subclinical, causes ‘sickness behaviours’ in animals characterized by reduced affective and social motivation, increased anxiety, avoidance of novel situations, repetitive behaviours, reduced exploration, self-imposed dietary restrictions and many other symptoms that mirror those seen in autism (Kohman et al., 2008; Johansson, 2012; Yee and Prendergast, 2011).

Similarly, the presentation of patients suffering from chronic inflammatory or autoimmune disease, or undergoing cytokine therapy, demonstrates that

**Abnormal bacterial flora and gastrointestinal comorbidities in ASD**

Gastrointestinal problems are a commonly found in autism and may be related to problem behaviours, sensory oversensitivity, dysregulated sleep, anxiety and irritability (Kjelte et al., 2011; Mazurek et al., 2012; Schumern et al., 2012; Chandler et al., 2013). Results from a large-scale population-based study conducted by the US Centers for Disease Control and Prevention showed that children with autism, in addition to many other unmet health needs, were twice as likely as children with ADHD, learning disability or other developmental delays, to have experienced frequent diarrhoea and/or colitis during the past year. They were also seven times more likely to have experienced these gastrointestinal problems than typical controls (Scheive et al., 2012).

Over the past several years there has been an increased recognition of gastrointestinal comorbidities among individuals with autism, including increased intestinal permeability, diarrhoea, constipation, gastrointestinal reflux, digestive enzyme deficiency and bacterial dysbiosis (Horvath et al., 1999; Wasilewski et al., 2009; de Magistis et al., 2010; Kucheki et al., 2006; Williams et al., 2011; Prondavessi and Napoli, 2012). 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 (Gorniolo et al., 2012).

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 (Adamset al., 2011, Wang et al., 2011; Gorniolo et al., 2012). An American Academy of Pediatrics consensus paper recommends that health care providers should be alerted to the

**CASE EXAMPLE 6**

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 slamming the screen. On examination he had marked tonsillar enlargement with marked erythema, and reactive anterior cervical lymphadenopathy. Bloods showed mildly raised inflammatory markers and elevated eosinophils. He was commenced on a gluten free diet and within two weeks his hyperactivity had decreased, he had ceased sleep disturbance and he was able to follow many commands. He was putting on weight. 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.

"The role of immune responses in the pathogenesis of gastrointestinal disorders in individuals with ASDs warrants additional investigation."

Consensus Report, American Academy of Pediatrics, Buie et al., 2010
**Medical Comorbidities in Autism Spectrum Disorders**

### CASE EXAMPLE 7

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.

Behavioral manifestations of gastrointestinal disorders in patients with autism, “as those can be atypical and evident only as a change in behaviour, thus presenting a significant challenge to both parents and health care providers.” (Furuta et al., 2012). This consensus paper identified that, in children with ASDs:

1. subtle or atypical symptoms might indicate the presence of constipation;
2. screening, identification, and treatment through a deliberate approach for underlying causes of constipation is appropriate;
3. diagnostic-therapeutic intervention can be provided when constipation is documented;
4. careful follow-up after any intervention should be performed to evaluate effectiveness and tolerance of the therapy.

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 (Buele et al., 2010). Because autonomic disturbances are common in autism, the posturing and guarding responses typically seen in non-ASD children with abdominal disease might be decreased in individuals with autism. Practitioners need to bear in mind the high mortality rate from digestive diseases in autism.

In another paper, the American Academy of Pediatrics stresses the need for appropriate investigations:

> "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 autism 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 (Finegold et al., 2002; Paranchio et al., 2005; Elkel et al., 2010; Finegold et al., 2010; Williams et al., 2012). Autistic traits (MacFabe et al., 2011; Willette et al., 2011; Baharnoori et al., 2012; El-Ansary et al., 2012). Subclinical gastrointestinal infections, such as Small Intestinal Bacterial Overgrowth are known to induce anxiety and aberrant behaviours in previously healthy adult animals (Lyte et al., 1998; Lyte et al., 2006).

Oxidative stress, acquired mitochondrial dysfunction and metabolic abnormalities in ASD

There is increasing evidence that mitochondrial dysfunction, perturbation in sulfur and amino acid metabolism, and high levels of oxidative stress are common in persons affected by autism. Elevations in metabolic markers of oxidative stress as well as reduced levels of glutathione and other cellular antioxidants have been found in many areas of the body, including the brain and primary immune cells (Chuaun et al., 2012; Ghanizadeh et al., 2012; Rose et al., 2011; Rose et al., 2012). 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.

A substantial percentage of autistic patients 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; Oliveira et al., 2005; Frye et al., 2013). In the majority of cases this abnormal energy metabolism cannot be linked to specific inborn mitochondrial disease, or another genetic cause of metabolism. It has therefore been suggested that in autism, abnormalities in mitochondrial function could be a downstream consequence of immune dysfunction (Palmeini and Persico, 2010; Rossignol and Frye, 2011). Insufficient mitochondrial energy production could both result from and contribute to cellular oxidative stress and chronic inflammation in autism.

Raising antioxidant levels and/or metabolic precursors and supporting mitochondrial function have been proposed as treatment avenues. Small clinical trials of antioxidants such as carnosine and

---

**CASE EXAMPLE 9**

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 AST of 900 (with EBR of 12 and platelets of 350). Rheumatoid Factor was markedly elevated at 104 (nv <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.

"Perpetuating the myth of autism as a primarily genetic disorder is a disservice to those who might benefit from treatment and divers attention from nongenetic causes." Prof Richard Deth, Northeastern University, Boston
N-acetyl-l-cysteine, mitochondrial agents such as carnitine, and metabolic precursors such as methylcobalamin and folinic acid have shown promising results in autism (Ghez et al., 2002; James et al., 2009; Rossignol and Frye, 2011; Ghanizadeh et al., 2012; Hardan et al., 2012).

**Autonomic nervous system dysfunction (dysautonomia) in ASD**

In recent years, an increasing number of researchers and clinicians have focused their attention on abnormalities of the autonomic nervous system (ANS) within the ASD population.

Elevated sympathetic and lowered parasympathetic activity is frequently present in children and adults with autism whether or not they have more obvious outward symptoms or signs of autonomic abnormalities (Tochi and Kamiio, 2003; Ming et al., 2005; Fan et al., 2009; Patriquin et al., 2011; Cheshire, 2012; Daluwatte et al., 2012).

It has been suggested that manipulating autonomic function could be a possible treatment avenue for aggression, anxiety and irritability, as well as the core symptoms of autism and cognitive functioning (Ratey et al., 1987; Narayan et al., 2010; Beverdorff et al., 2011; Bodner et al., 2012). Following very promising pilot trials on adults with autism, which demonstrated that adrenergic antagonist propranolol improves the core features of the disorder, such as impaired social interaction and communication, randomised controlled trials are currently underway at the University of Missouri, MU Thompson Center for Autism and Neurodevelopmental Disorders.

**Seizure disorders in ASD**

Prevalence of seizure disorders is significantly higher in people with ASD than is the norm and epilepsy is a contributing factor to the elevated mortality risk seen in autism, making detection and treatment of this medical comorbidity in autism of utmost importance (Hughes and Melyn, 2005; Mournside et al., 2011). This is especially relevant in the context of subclinical epileptiform activity being found in a majority of individuals with autism, even in the absence of clinical seizure disorder. When epileptiform activity is present in the ASDs, therapeutic strategies such as antiepileptic drugs, steroids, and even neurosurgery aimed at its control can often lead to a significant improvement in language and autistic behaviours, in addition to reducing seizure activity (Levine et al., 1999; García-Peñas, 2005; Muñoz-Yunta et al., 2008).

“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.”


**Medical Considerations**

**Approaching comorbidity in the ASD patient:**

*Up until recently, scientific consensus suggested autism progresses to a predetermined outcome regardless of medical intervention. Advice to patients, guardians and the wider audience has reflected such consensus. Now the consensus has changed, and so must the awareness.*

Until more definitive answers pertaining to the pathophysiology of autism are available, frontline physicians are charged with treating, as best as they can, whatever medical illnesses a patient may have, whether they be comorbid, or part of the underlying pathology. The importance and value of such treatment has been highlighted by recent authoritative studies.

Managing comorbid illness in the autistic patient carries a multitude of challenges. Communicating pain, processing pain or tenderness, level of baseline agitation, lack of a coherent history, and other factors can all contribute to a challenging assessment. In all likelihood, such challenges reflect the substance respiratory, gastrointestinal and neurological morbidity and mortality rates that are consistently reported.

The chart below is an attempt to improve recognition of common problems encountered when autistic patients present with comorbid health issues. These recommendations may seem somewhat basic considerations when dealing with a communication-challenged patient of any age, however, increasing reports of premature attribution of physical health issues to the autism phenotype and the consequences thereof, make it prudent to highlight the following:

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

2. **Pain can be acute or chronic, progressive or static.**

3. **Common sources of pain and discomfort include:**
   - Headache
   - Earache
   - Toothache
   - Sore Throat
   - Reflux
   - Oesophagitis
   - Gastritis
   - Colitis
   - Soft or hard stool constipation (underlying cause will be relevant)
   - Small Intestinal Bacterial Overgrowth
   - Musculoskeletal injury or disease
   - Seizure Disorder (including subclinical crisis*)
   - Allergy Disorder

* from Bag et al., 2010. ** from Munoz-Yunta et al., 2008.
Medical Comorbidities in Autism Spectrum Disorders

Conclusion

Medical comorbidities are much more prevalent and difficult to recognize in patients with autism than in the general population. The failure to identify such comorbidities is due in part to communication impairments and ambiguous symptomatology, but widespread under-diagnosis is also the result of commonly held beliefs that aberrant behaviours and symptoms are ‘just a part of autism’. As a result, these pathologies are often left untreated.

All of the discussed medical comorbidities and consecutive pathological processes can negatively impact behaviour, socialisation, communication, cognitive function and sensory processing of individuals with autism. It is also becoming increasingly clear that the medical abnormalities that underlie autism are not stagnant or transient, but tend to be chronic and in many cases, if left unreognised and untreated, progressive. Average diagnosis and treatment often results in improved level of functioning and decreased severity of symptoms. Recognition that problem behaviours might indicate an underlying medical condition will facilitate diagnosis and treatment and ultimately improve the quality of life for many individuals with autism. As well, correctly identifying and addressing medical comorbidities in autism will help reduce the immense emotional, physical and financial burden on families and carers, and is fiscally responsible to the wider society.

Children and adults with autism have an increased need for medical care and/or specialist services, both for their core functional deficits and concurrent medical conditions. Appropriate and individualised medical assessment must be carried out in all cases, including a documented clinical examination.

References


Ivan is a 5-year old boy with regressive autism. He developed normally as a baby, including normal speech and ability to play with toys. However, his speech started to slow down around 24 months of age. Stools started to become mushy, malodorous, and light in colour. Ivan suffered from recurrent Herpes infection 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 PA N D A S, and is reported as doing well.

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 discomfort. 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.

Ivan, a 5-year old boy with regressive autism. He developed normally as a baby, including normal speech (bilingual) development. He started presenting with unusual behaviours at 18 months, including tip-toe walking, hand flapping, motor stereotypes. Last 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 has developed onset of irritability, hyperactivity, sleep disturbance and occasional incontinence. His obsessional behaviours were marked. He was seen by a rheumatologist consultant, who undertook bloods. ASOT and Anti-DNAs 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.
Medical Comorbidities in Autism Spectrum Disorders


“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.”
Consensus Report, American Academy of Pediatrics, Buie et al., 2010

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

“We need to empower primary care physicians to know that they already have the skill set to work with children who have autism… Doctors can address these co-occurring behaviors head-on. It will make a positive difference.”
Darryn M. Sikora, PhD. pediatric psychologist, Providence Child Center

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

“Sudden and unexplained behavioral change can be the hallmark of underlying pain or discomfort. Behavioral treatment may be initiated as the possible concurrent medical illness is being investigated, diagnosed (or excluded), and treated, but the behavioral treatment should not substitute for medical investigation.”
Consensus Report, American Association of Pediatrics, Buie et al. 2010

ISBN: 978-0-9575787-0-8