ISSN 2219-2808 (online)

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2021 May 9; 10(3): 15-47

Published by Baishideng Publishing Group Inc

WJCP

World Journal of Clinical Pediatrics

Contents

Bimonthly Volume 10 Number 3 May 9, 2021

World Journal of Clinical Pediatrics

Bimonthly Volume 10 Number 3 May 9, 2021

Contents

ABOUT COVER

Peer reviewer of *World Journal of Clinical Pediatrics*, Theofilos M Kolettis, MD, PhD, Professor of Cardiology, University of Ioannina, Chief, 1st Department of Cardiology, University Hospital of Ioannina, Ioannina, 1 St. Niarxou Avenue, 45500 Ioannina, Greece. thkolet@uoi.gr

AIMS AND SCOPE

The primary aim of the *World Journal of Clinical Pediatrics* (*WJCP*, *World J Clin Pediatr*) is to provide scholars and readers from various fields of pediatrics with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCP mainly publishes articles reporting research results and findings obtained in the field of pediatrics and covering a wide range of topics including anesthesiology, cardiology, endocrinology, gastroenterology, hematology, immunology, infections and infectious diseases, medical imaging, neonatology, nephrology, neurosurgery, nursing medicine, perinatology, pharmacology, respiratory medicine, and urology.

INDEXING/ABSTRACTING

The *WJCP* is now abstracted and indexed in PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Pediatrics

ISSN
ISSN 2219-2808 (online)

LAUNCH DATE
June 8, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Toru Watanabe, Consolato M Sergi

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2219-2808/editorialboard.htm

PUBLICATION DATE
May 9, 2021

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2021 May 9; 10(3): 15-28

DOI: 10.5409/wjcp.v10.i3.15

ISSN 2219-2808 (online)

EDITORIAL

Autism medical comorbidities

Mohammed Al-Beltagi

ORCID number: Mohammed Al-Beltagi 0000-0002-7761-9536.

Author contributions: Al-Biltagi M wrote and revised the whole manuscript.

Conflict-of-interest statement: The author declares that he has no conflict of interests for this article.

Manuscript source: Invited manuscript

Specialty type: Pediatrics

Country/Territory of origin: Bahrain

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0

Mohammed Al-Beltagi, Department of Pediatrics, University Medical Center, King Abdulla Medical City, Arabian Gulf University, Manama P.O. Box 26671, Bahrain, Bahrain

Mohammed Al-Beltagi, Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta 0000000, Al Gharbia, Egypt

Corresponding author: Mohammed Al-Beltagi, MD, PhD, Chairman, Professor, Department of Pediatrics, University Medical Center, King Abdulla Medical City, Arabian Gulf University, King Abdulaziz Avenue, Manama P.O. Box 26671, Bahrain. mbelrem@hotmail.com

Abstract

Medical comorbidities are more common in children with autism spectrum disorders (ASD) than in the general population. Some genetic disorders are more common in children with ASD such as Fragile X syndrome, Down syndrome, Duchenne muscular dystrophy, neurofibromatosis type I, and tuberous sclerosis complex. Children with autism are also more prone to a variety of neurological disorders, including epilepsy, macrocephaly, hydrocephalus, cerebral palsy, migraine/headaches, and congenital abnormalities of the nervous system. Besides, sleep disorders are a significant problem in individuals with autism, occurring in about 80% of them. Gastrointestinal (GI) disorders are significantly more common in children with ASD; they occur in 46% to 84% of them. The most common GI problems observed in children with ASD are chronic constipation, chronic diarrhoea, gastroesophageal reflux and/or disease, nausea and/or vomiting, flatulence, chronic bloating, abdominal discomfort, ulcers, colitis, inflammatory bowel disease, food intolerance, and/or failure to thrive. Several categories of inborn-errors of metabolism have been observed in some patients with autism including mitochondrial disorders, disorders of creatine metabolism, selected amino acid disorders, disorders of folate or B12 metabolism, and selected lysosomal storage disorders. A significant proportion of children with ASD have evidence of persistent neuroinflammation, altered inflammatory responses, and immune abnormalities. Anti-brain antibodies may play an important pathoplastic mechanism in autism. Allergic disorders are significantly more common in individuals with ASD from all age groups. They influence the development and severity of symptoms. They could cause problematic behaviours in at least a significant subset of affected children. Therefore, it is important to consider the child with autism as a whole and not overlook possible symptoms as part of autism. The physician should rule out the presence of a medical condition before moving on to other interventions or therapies. Children who enjoy good health have a better chance of learning. This can apply to all children including those with autism.

Grade E (Poor): 0

Received: January 23, 2021
Peer-review started: January 23, 2021
First decision: February 12, 2021
Revised: February 12, 2021
Accepted: March 17, 2021
Article in press: March 17, 2021
Published online: May 9, 2021

P-Reviewer: Ding N, Sergi CM
S-Editor: Gao CC
L-Editor: A
P-Editor: Yuan YY

Key Words: Autism; Children; Medical comorbidity; Epilepsy; Sleep disorders; Allergy; Gastrointestinal diseases

Core Tip: Medical comorbidities are common in children with autism. Some genetic disorders are more common in children with autism spectrum disorders. Medical comorbidities have a significant impact on the child's behaviour and development. Early identification and treatment of these comorbidities will help to improve the child's ability to learn and improve his or her circumstances and those of his or her family.

Citation: Al-Beltagi M. Autism medical comorbidities. *World J Clin Pediatr* 2021; 10(3): 15-28
URL: https://www.wjgnet.com/2219-2808/full/v10/i3/15.htm
DOI: https://dx.doi.org/10.5409/wjcp.v10.i3.15

INTRODUCTION

Comorbidity is the presence of one or more additional diseases or disorders that coincide with a primary disease or disorder. A comorbid condition is a 2nd order diagnosis that has core symptoms that are distinct from the primary disorder. Comorbidity is much more common in people with autism spectrum disorders (ASD) than in the general population. For example, patients with autism are 1.6 times more likely to have eczema or skin allergies, 1.8 times more likely to have asthma and food allergy, 2.1 times more likely to have frequent ear infections. 2.2 times more likely to have severe headaches, 3.5 times more likely to have diarrhoea or colitis, and 7 times more likely to report gastrointestinal (GI) problems[1].

A child with autism may have symptoms of other comorbidities in addition to the core symptoms of autism (*e.g.*, social deficits, language impairment, repetitive behaviours, *etc.*). Recognising these medical conditions is important because many of the medical conditions could stimulate or exacerbate the abnormal behaviour that occurs in children with autism. Once these medical conditions are treated, the behaviours stop. Because unwell people do not perform adequately, some children with autism may lose skills and/or fail to retain skills because of their medical conditions. Effective learning requires a healthy state. Comorbid conditions may be markers of the underlying pathophysiology and require a more sophisticated therapeutic approach. In the meantime, it is more likely that the increased mortality risk associated with ASD is related to the presence of comorbid medical conditions and intellectual disabilities than to ASD itself. Since most of them are treatable, the treatment of comorbid medical conditions can lead to a substantial improvement in the quality of life of the child and the family[2,3]. However, it is not always easy to identify comorbid conditions in children with ASD due to several factors, such as communication disorders, the ambiguity of symptoms, their deviation from those in the general population, or their change over time. These factors are also compounded by the widespread belief that deviant behaviours and symptoms are 'just part of autism'. The lack of diagnostic tools available to screen for these disorders is another important limitation[4]. Many symptoms and behaviours commonly attributed to autism, may reflect the presence of other organic disorders. For example, headbanging could be due to the presence of headaches, or pain when frustrated and the inability to communicate these symptoms. If the child fidgets frequently, he or she could have complaints related to constipation. Aggression and self-injurious behaviour could also be related to the presence of the pain and the child's inability to communicate about his/her condition. Pica could also be a sign of nutrient deficiencies, particularly iron, which is relatively common in children with autism. Food refusal may be related to the high food selectivity observed in children with autism but could also reflect the presence of food allergy or intolerance or be due to a more local cause such as the presence of dental problems[5]. Table 1 showed the different comorbidities that could present in children with autism.

Table 1 Autism comorbidities

Related disorders
Anxiety disorder
Obsessive-compulsive disorders
Attention deficit hyperactivity disorders
Mood disorders
Sleep disorders: Difficulty falling asleep, inability to sleep in a flat position, nighttime reawakenings, sleepwalking
Epilepsy
Systemic medical disorders
Accidents
Injuries, drowning, suffocation, *etc.*
Genetic disorders
Fragile X syndrome, Down syndrome, Duchenne muscular dystrophy, neurofibromatosis type I, and tuberous sclerosis complex
Metabolic disorders
Mitochondrial disorders, disorders of creatine metabolism, selected amino acid disorders, disorders of folate or vitamin B12 metabolism, and selected lysosomal storage disorders
Endocrine disorders
e.g., hypothyroidism
Neurological disorders
Congenital abnormalities of the nervous system, epilepsy, macrocephaly, hydrocephalus, cerebral palsy, migraine/headaches, paralytic muscular disorders like Duchenne muscular dystrophy, increase in sympathetic and a decrease in parasympathetic activity, and dysautonomia
Immune dysfunction
Neuroinflammation, immune deficiency and dysfunction
GI disorders
Chronic constipation, chronic diarrhea, eosinophilic esophagitis, gastroesophageal reflux and/or disease, nausea and/or vomiting, chronic flatulence, abdominal discomfort, ulcers, colitis, inflammatory bowel disease, food intolerance, and/or failure to thrive
Feeding disorders
Selective eating, difficulty swallowing, abnormal behaviors during meals such as ritualistic behaviour, throwing tantrums or gagging and vomiting
Allergic disorders
Asthma, nasal allergies, atopic diseases (immunoglobulin E-mediated), food allergies and intolerances
Toileting problems
Difficulties in learning how to use the toilet during the day and at night, knowing when they need to use the toilet, communicating the need to use the toilet, being able to get to the toilet independently or in time, learning to use different toilets with which they are unfamiliar, wiping themselves, sensory differences (dislike of the noise made by toilets, the sensation of passing urine/faeces, a cold toilet seat, or a preoccupation with water in the toilet), smearing faeces, a range of continence-specific difficulties, including bowel or bladder difficulties such as bedwetting and constipation

GENETIC DISORDERS

Certain known genetic disorders are associated with an increased risk of autism, including but not limited to Fragile X syndrome (FXS), Down syndrome (DS), Duchenne muscular dystrophy, neurofibromatosis type I (NF1), and tuberous sclerosis complex (TSC). It may be useful to view ASD as a cloud, representing the interaction of several different genetic and other etiologies that end with abnormal brain wiring. FXS is the most common cause of inherited intellectual disability; characterized by the presence of abnormal patterns of neural "wiring" or connectivity that leads to ASD symptoms, including impaired communications. FXS is the most common-known single-gene disorder in all ASD cases. It has been observed that about 2%-3% of all children with ASD cases have FXS, and about 25%-33% of FXS patients have ASD. Children with both FXS and ASD have higher rates of social anxiety, intellectual disability, hyperarousal, repetitive behaviors, and other FXS-related differences than those with ASD of unknown cause[6].

Only a small number of children with ASD may also have DS as DS is uncommon and occurs in only 1/800 births. On the other hand, ASD is relatively common in children who have DS; up to 40% of children with DS also have ASD[7]. Children with DS-ASD were more likely to have a history of developmental regression, including loss of language and social skills, poor communication skills (many children did not have meaningful speech or singing), self-injurious and disruptive behaviors (such as skin pulling, biting, and head hitting or banging), repetitive motor behaviors (such as teeth grinding, hand flapping, and rocking), unusual vocalizations (such as grunting, humming, and guttural sounds), unusual sensory responses (such as spinning, staring at lights, or sensitivity to certain sounds), feeding problems, (such as food refusal or strong preference for certain textures), increased anxiety, irritability, difficulty with transitions, hyperactivity, attention problems, and significant sleep disturbances[8,9]. Children with DS and ASD are more prone to other comorbidities such as congenital heart defects, anatomical abnormalities of the GI tract, neurological findings (*i.e.*, seizures, dysphagia, severe hypotonia, and motor delays), ophthalmological problems, and respiratory problems (*i.e.*, pneumonia and sleep apnea)[10].

There is a high prevalence of ASD in patients with dystrophinopathies. Duchenne muscular dystrophy is not only a muscle disease but also a disease that affects the brain. Any child with autism who has toe-walking should have creatine phosphokinase (CPK) levels determined to rule out Duchenne muscular dystrophy[11,12]. Some studies have shown that symptoms of autism are increased in patients with NF1, as well as a significant co-occurrence with symptoms of attention-deficit/hyperactivity disorder (ADHD)[13,14]. However, a recent study by Morotti *et al*[15] showed that only ADHD, not ASD, was more common in children with NF1 than in the general child population. They related the notion of increased ASDs in NF1 to increased use of autism questionnaire scores due to co-occurring ADHD symptoms. They found that adaptive behavior in patients with NF1 showed normal socialization but lower communication skills. TSC is a rare genetic multisystem disorder characterized by hamartoma formation in multiple organs and systems. It is one of the main syndromes associated with ASD; with a prevalence of ASD ranging from 26% to 45%. Therefore, children with TSC have an increased risk of developing ASD, which depends on the presence of several factors, including brain lesion burden, prominent lesion type, the tuber size and location, cyst-like tubers, presence of a *TSC2* mutation, early-onset and refractory seizures, and the presence and severity of cognitive impairment. Consequently, early termination of seizures may improve the neuropsychiatric outcome, at least in some cases[16,17]. Because of the increased incidence of genetic disorders in children with autism, any child diagnosed with ASD should have a consultation with a geneticist. Currently, there are therapeutic interventions for many of the genetic disorders that can help guide the treatment pathway and make a significant difference in helping children reach their full potential.

NEUROLOGICAL DISORDERS

Children with autism are more likely than the general population to have several neurological disorders, including epilepsy, macrocephaly, hydrocephalus, cerebral palsy, migraine/headaches, and congenital abnormalities of the nervous system. The behaviours of autism overlap with a variety of different neurological disorders, suggesting common molecular mechanisms[18]. Epilepsy is a brain disorder characterised by episodic, unpredictable changes in mental status with recurrent seizures or convulsions. Epilepsy, like autism, is increasingly described as a spectrum disorder. Up to 60% of children with autism have abnormal electroencephalogram (EEG), compared with 6%-7% in normal children and 10% to 30% of children with autism have epilepsy. At the same time, up to 8% of epileptic children have ASD. Therefore, autism is considered as a comorbidity to epilepsy, and epilepsy is considered as a comorbidity to autism. Both may occur together[19]. Severity of seizure activity varies from grand mal to subtle activities such as rapid eye blinking, zoning out, inattention for prolonged periods; with/without disturbed consciousness or even epileptic encephalopathies. At the same time, there is an increased incidence of epilepsy, autism, and intellectual disability simultaneously in some neurological disorders[20]. Infantile spasms have a high rate of intellectual disability and deficits in social communication are lower than expected for the child's intelligence or developmental quotient. Approximately 10%-15% of children with infantile spasms develop autism. A history of spasms is found in 6% of all children with ASD[21]. Children with TSC have very high rates of both epilepsy and ASD (40%). ASD is higher in children with

intellectual disability and the risk for ASD increases especially in children with epilepsy and with temporal lobe brain lesion[22]. Other neurological syndromes associated with high rates of both ASD and epilepsy include FXS, *CDKL5* gene (responsible to making a protein needed for normal brain development), Rett syndrome, and Angelman' syndrome.

The co-occurrence of epilepsy and autism is due to the presence of common pathogenic mechanisms. Synucleinopathy (abnormal accumulation of aggregates of alpha-synuclein protein in neurons, nerve fibers, or glial cells), synaptopathies (dysfunction of synapses in the brain, spinal cord, or peripheral nervous system), excitopathies (tetrad from epilepsy, ataxia, **s**ensorineural deafness, and a renal salt-wasting **t**ubulopathy), channelopathies, inflammation, and abnormal glial cell interaction are common underlying pathogenic mechanisms for autism and epilepsy[23]. Early-childhood seizures may also induce "autism-like" behaviour in rodents. Increased excitability in the developed brain causes impaired plasticity which in turn induces both cognitive deficits, autism, and epileptogenesis. Seizures, impaired neuroplasticity, and autism-like behaviours appear to cluster during early brain development, which may indicate a link between them[24]. Understanding and harnessing these relationships may help in autism treatment and biomarker discovery. The risk of developing epilepsy in children with ASD increases with the presence of intellectual disability, and with female gender. The risk of epilepsy in children with intellectual disability without autism is about 21.4%, which increases to 50% when both autism and intellectual disability are present. The risk of epilepsy also increases in the presence of temporal lobe pathology secondary to conditions such as TSC[25]. Distinguishing between seizures and seizure-free activities is challenging in children with autism, especially in the presence of learning disabilities and communication difficulties. Odd behaviours, stereotypy, aggressive behaviour, neurological deficits, self-injurious behaviour, and decreased responsiveness may be present in children with autism, whether they have epilepsy or not. Seizures can often manifest in various subtle ways, features, or behaviours that confound distinction between seizure-related from non-seizure related behaviours[26]. Therefore, any child with autism should be evaluated for the presence of seizures with an EEG for 24 h or longer by a paediatric neurologist. A video EEG is strongly recommended when autism is present with high intellectual disability (50% will have epilepsy) and when autism is associated with secondary conditions such as Angelman syndrome, DS, or tuberous sclerosis. Parents, friends, therapists, family members, and caregivers should know the signs, what a seizure looks like, and possible precursors to a seizure. It is also important to know that seizures can be fatal. If the child has recordable seizure activity, it is medically necessary to treat the seizure disorder[27].

Autonomic nervous system dysfunction is common in children with ASDs. An increase in sympathetic and a decrease in parasympathetic activity are commonly present in children and adults with ASDs, with/without the presence of obvious symptoms and/or signs of autonomic abnormalities. This autonomic imbalance may be evident in changes in heart rate and its variability, mean arterial and diastolic blood pressure, atypical pupillary light reflex, atypical autonomic response to anxiety, elevated plasma levels of nor-epinephrine suggestive of a chronic state of sympathetic nervous system hyperactivity, and lower baseline respiratory sinus arrhythmia suggestive of reduced vagal modulation[28]. Toe-walking is one of the common stereotypic motor movements observed in children with autism, aiming to reduce sensory overstimulation in the feet caused by walking on the whole foot. However, it could be related to the presence of motor coordination difficulties, a tight Achilles tendon, or a sensory processing difference. Toe-walking is also seen in other neurological or developmental disorders, such as cerebral palsy, and paralytic muscular disorders like Duchenne muscular dystrophy. Any child with autism who has toe-walking should have a CPK level to rule out Duchenne muscular dystrophy[29].

Toileting is an important skill necessary for independent living. Therefore, incontinence is a significant barrier to good quality of life for people with autism. Lower cognition and verbal levels correlate significantly with the age at which bowel and urine training is completed in children with autism[30]. Approximately 30% of children with autism have anxiety related to toileting, with verbally impaired individuals having the most. Children with autism have potty training problems due to sensory hypersensitivity, communication problems, self-confidence problems, and short-attention-span. The most common problems with toileting were urinating in places other than the toilet, constipation, clogging the toilets, constant flushing, and smearing. Unfortunately, children with toilet training problems are at more risk of public embarrassment, punishment, and loss of self-esteem. In addition, children who do not use the toilet by age 5 tend to lose control of their bladder. Children with lower

adaptive functioning were associated with greater toileting problems[31,32].

SLEEP DISORDERS

Sleep disorders are significant problems in individuals with autism, present in about 80% of them. Sleep disturbances are one of the most common concerns reported by parents of children with autism; because sleep affects not only the children, but their families as well. Sleep problems can cause difficulty falling asleep, inability to sleep in a flat position, nighttime reawakenings, sleepwalking, learning problems, hyperactivity, inattention, anxiety, aggression, and various health problems. It could be due to hormonal imbalances, GI disorders, seizure activity, poor sleep environment, sleep apnea, or as a side effect of some medications commonly used to treat autistic symptoms. Polysomnographic studies of children with ASD showed that most of their abnormalities are related to rapid eye movement sleep (REM), which includes decreased quantity, increased undifferentiated sleep, immature organization of eye movements into discrete bursts, decreased time in bed, total sleep time, REM sleep latency, and increased proportion of stage 1 sleep[33]. The sleep community has identified autism as a priority population for targeted interventions for sleep disorders. Poor sleep affects the health of the individual and daily functioning, as well as the integrity of the family. Sleep disorders are highly treatable. Therefore, evidence-based standards of care for monitoring, assessing, and treating sleep disorders in children with ASDs are of great importance[34]. Sleep disorders have been found to be associated with GI dysfunction in children with ASDs. About 24.5% of a sample of children with ASDs had both chronic GI symptoms and sleep problems. Chronic GI symptoms were independently associated with increased sleep disturbance. Sleep problems were most common in children with GI symptoms (50%) than in children without (37%)[35,36]. Poor sleep causes a higher percentage of behavioural problems (such as stereotypy and self-injurious behaviour) than observed with good sleep. Medication use, sleep problems, and anxiety explained 42% of the variance in challenging behaviour, with sleep problems being the strongest predictor. Stereotypic behaviour may be predicted in the presence of fewer hours of sleep per night and crying at night[37]. The implementation of non-pharmacotherapeutic interventions such as bedtime routines and sleep-appropriate approaches is the mainstay of behavioural management. Treatment strategies along with limited regulated pharmacotherapy can help improve the quality of life of children with ASD and have a positive effect on the family[33].

GI DISORDERS

GI Problems are significantly more common in patients with ASD, occurring in 46% to 84% of autistic children. The most common GI problems observed in children with ASD are chronic constipation, chronic diarrhoea, gastroesophageal reflux and/or disease, nausea and/or vomiting, chronic flatulence, abdominal discomfort, ulcers, colitis, inflammatory bowel disease, food intolerance, and/or failure to thrive. Food allergies are more common in children with ASDs, reaching up to 20%-25% compared to 5%-8% in the general paediatric population[38]. Common mechanisms for GI disorders in children with ASDs include immune dysfunction, gut inflammation, microbiota dysregulation and dysbiosis, dietary metabolites, and/or dysautonomia. Insistence on sameness can lead sufferers to demand stereotypical diets, that can lead to inadequate intake of fiber, fluids and other foods, which can cause GI symptoms. Some medications can affect bowel function; for example; stimulants can cause abdominal pain, and βeta-blockers can cause diarrhoea, constipation and stomach irritation[39].

These GI disorders can cause pain and discomfort to and interfere with learning in individuals with ASD. Unrecognized GI disorders; specifically reflux esophagitis and disaccharide malabsorption may contribute to behavioural problems in children with nonverbal autism. These behavioural problems may present as posturing, self-injury, or outbursts with no apparent causes. Unfortunately, these manifestations can be overlooked as a behavioural problem rather than a medical condition, especially since many children with autism are unable to effectively communicate their symptoms or express discomfort to their doctors. Lactase deficiency not associated with intestinal inflammation or injury is common in children with autism and may contribute to abdominal discomfort, pain, and observed behavioural problems[40]. At the same

time, GI symptoms are difficult to diagnose in ASD because there are no clinical practice guidelines that provide for routine consideration of possible GI symptoms or other medical conditions in patients with ADS. These guidelines are especially needed because many individuals with ASD are nonverbal and cannot express pain or discomfort through language, and they cannot communicate symptoms as clearly as their typically developing peers. Even those who can communicate verbally may have difficulty describing subjective experiences or symptoms. Healthcare professionals should consider the possibility of the presence of GI dysfunction in patients with ASD, especially those who present with odd postures or movements, sleep disturbances, food intolerances, and aggressive or self-injurious behaviours. For this reason, clinicians should obtain a proper GI/nutritional history that includes eating patterns, presence of allergies and food intolerances, and stool patterns[41]. Sleep history is very important as many underlying GI disorders can manifest in sleep pattern[36]. Clinicians should review the child's growth across the lifespan, medication, and sleep history. They should also be able to identify vocal or motor behaviours that may reflect the presence of pain or GI disorders. Common vocal behaviours that may be associated with the presence of GI disorders (such as gastroesophageal reflux disease, eosinophilic esophagitis, or allergic esophagitis), including but not limited to throat-clearing behaviours, guttural vocalizations, spitting up in infants, ear rubbing, habitual coughing, and/or difficulty swallowing. Motor behaviours associated with the presence of GI disorders include seeking belly pressure, some pointing behaviours, neck or body posture, certain repetitive behaviours, aggressive or self-injurious behaviours. There is a strong correlation between aggressive behaviours and underlying GI disorders[42].

The strong correlation of GI symptoms with the autism severity suggests that children who have more severe autistic features are more likely to have severe GI symptoms. Symptoms of GI disorder are more likely to be associated with sleep disturbances and food intolerances. Therefore, it is important to consider this association when assessing and treating these comorbidities. Clinicians should screen for constipation, diarrhoea, or soiling of underwear in children with ASD who have prominent rigid–compulsive symptoms[43]. Paediatricians should refer children with autism for GI evaluation in the presence of eczema, vocal or motor signs, aggressive or self-injurious behaviours, chronic constipation or diarrhoea, and chronic spitting or vomiting. Increased intestinal permeability is a common finding in children with ASD; especially those who present with GI symptoms. Although it is a real challenge, measurement of intestinal permeability can be done by measuring plasma zonulin level, which is a valuable blood marker to evaluate abnormal intestinal permeability[44]. Endoscopy may reveal signs of allergic esophagitis, acid reflux damage, allergic changes, or evidence of inflammatory bowel disease in patients with ASD and abdominal manifestations[45]. If the GI disorder is recognized and medical treatment is effective, the behavioural problem may improve. If abdominal pain or discomfort is a framing event, psychotropic medications are unlikely to be effective and may even exacerbate the problem if they have adverse GI effects. The emerging concept of a microbiota-gut-brain axis suggests that modulation of the gut microbiota may be a tractable strategy for developing new therapeutics for complex CNS disorders[46].

Despite studies finding no higher prevalence of celiac disease (CD) in ASD, one child per 68 children with CD will develop autism, and one child per 130 children with autism will develop CD. There is a strong association between CD—even in the absence of GI symptoms—and epilepsy, and cerebral calcifications, as well as positive responses to dietary changes in these patients. Investigation and treatment of CD, non-celiac gluten sensitivity (NCGS), and epilepsy—even in the absence of typical GI symptoms or overt seizures—could potentially yield good outcomes for patients with ASD[47]. Since children with ASD are more likely to have atopy and allergies, possible NCGS or wheat sensitivity must be considered in these children, especially if irritable bowel symptoms are present[48]. In children with unclear neurological manifestations with probable autoimmune etiology, transglutaminase-2 autoantibody titer should be determined considering the possibility of gluten sensitivity. The gluten-free diet remains the only effective treatment reported to date. Therefore, it should be recommended to all patients with gluten sensitivity, regardless of the type of manifestations. Medical professionals should be aware of the possibility of the presence of NCGS in some patients with ASD; especially those presenting with atopic disease, migraine, mood and anxiety disorders. Many children with autism do very well on a gluten-free, soy-free, and dairy-free diet. However, this diet should not be attempted until a celiac test has been performed[49].

METABOLIC DISORDERS

Metabolic disorders are inborn errors of metabolism (*i.e.*, a single-gene metabolic disorder) that can affect the synthesis or functions of proteins (*e.g.*, enzyme), fats, or carbohydrates, resulting in accumulation or deficiency of certain metabolites and consequently the appearance of certain symptoms and signs, depending on the metabolic pathway affected. Several categories of inborn errors of metabolism have been observed in some patients with autism including mitochondrial disorders, disorders of creatine metabolism, selected amino acid disorders, disorders of folate or vitamin B12 metabolism, and selected lysosomal storage disorders[50]. Mitochondrial dysfunction is one of the relatively common metabolic disorders in patients with autism. Recent studies have increasingly associated mitochondrial dysfunction with ASD, with a prevalence rate of 5% in patients with autism. Since the mitochondria are the "powerhouse of the cell" and produce most of the cellular energy, they play an integral role in various cellular functions, especially for the brain as it has very high energy demands. Consequently, mitochondria are prone to many insults, which explains how a variety of factors may contribute to a consistent behavioural phenotype in ASD[51].

Many clues could help to identify the presence of metabolic disorders in patients with ASD. Patients with metabolic disorders may have unexplained fatigue and usually become very ill (unusually lethargic) with prolonged recovery time from illnesses that do not usually cause significant illness. They may also have developmental regression during/after the illness. Metabolic disorders are usually multisystem disorders that affect many organs and present with various problems such as seizures, sensorineural hearing loss, renal tubular problems, or unexplained cardiac myopathy. It is important to look for signs of multisystem involvement such as growth abnormalities, abnormalities of head circumference and its change over time, possible cardiac involvement (*e.g.*, heart murmur), possible organomegaly or other abdominal pathology, hypermobile or stiff joints, and signs of possible autonomic dysfunction. Neurologic manifestations are very common in inborn errors of metabolism. Common neurological manifestations include developmental or neurologic regression, encephalopathy, seizures, abnormal ocular findings including extraocular movement, abnormalities of muscle tone (hypotonia, hypertonia, and dystonia), abnormalities of deep tendon reflexes, and movement disorders (*e.g.*, ataxia, myoclonus)[52,53].

Some laboratory findings may help predict the presence of comorbid metabolic disorders in children with autism. Abnormal blood count such as anaemia, abnormal mean corpuscular volume (high in vitamin B12 or folate deficiency or disorders), neutropenia and/or thrombocytopenia could be a clue[54]. Abnormal blood chemistry is another important clue. It may include the presence of hypoglycaemia, hyperglycaemia, ketosis, hyperammonemia, lactic acidaemia, abnormal serum bicarbonate, abnormal anion gap, abnormal plasma amino acid levels, and abnormal lactate or pyruvate. Urine analysis may elaborate enormous information including the urine pH, urinary glucose, abnormal urinary organic acids such as lactic aciduria, elevated levels of Krebs cycle intermediates, 3-methyl glutaric acid, metabolites that suggest impaired mitochondrial fatty acid oxidation, or unexplained ketonuria. Almost one-third of children with autism have elevated plasma lactate and/or the lactate-to-pyruvate ratio, and elevated levels of many other mitochondrial biomarkers (pyruvate, carnitine, and ubiquinone) with significant differences between ASD and controls[55].

IMMUNE, AUTOIMMUNE, AND ALLERGIC DISORDERS

A significant proportion of children with ASD have evidence of persistent neuroinflammation, altered inflammatory responses, and immune abnormalities. Approximately 25% of children with ASD have immune deficiency and dysfunction. Most children with autism do not have symptoms of immune dysregulation, so it is important to perform laboratory testing to rule this out[56]. Children who have GI disorders are more likely to have immunodeficiency. Testing for immunodeficiency and dysfunction is very simple and inexpensive. Laboratory tests can include immunoglobulin G (IgG) subclasses, total IgG, and quantitative immunoglobulin[57]. To treat immunodeficiency, intravenous immunoglobulin could be given every 3-4 wk. With this treatment, some children with autism experience cognitive progress and improvement in language and social skills[58]. Some studies also showed that anti-brain antibodies may play an important pathoplastic mechanism in autism. Prenatal

and/or postnatal exposure to these antibodies may increase the severity of autism by impairing cognitive processes and adaptive functions, increasing motor stereotypies, altering the sleep-wake cycle, and delaying or halting neurodevelopment, especially as it relates to verbal and nonverbal language. Therefore, anti-brain antibodies can be used as biomarkers that predict the severity of autism and the clinical features of ASD; and potentially provide new avenues for preventive and therapeutic strategies[59]. At the same time, children with autism who have high titers of seropositive systemic antibodies should be clinically followed up at regular intervals to detect the possible development of symptoms and signs of systemic autoimmune diseases. In the meantime, treatment of CNS or peripheral infections, such as those in the GI system or sinuses, calming of autoimmune responses, or discontinuation of therapy with inflammation-inducing agents often leads to reversal and normalization of behaviours, and restoration of normal brain function[60].

Allergic disorders are significantly more common in people with ASD from all age groups. They influence the development or severity of symptoms and induce problematic behaviours in at least a subset of the affected individuals. Various allergic manifestations such as asthma, nasal allergies, atopic diseases (IgE-mediated), food allergies and intolerances may occur in children with ASD[61]. There is a positive association between the frequency and severity of allergic manifestations and the severity of autism. Discomfort and pain associated with allergic conditions exacerbate behavioural symptoms. Allergic neuroimmune activation may, in some cases, underlie core autism symptoms and behavioural problems. Therefore, treatment of allergies can lead to improvement in negative and challenging behaviours and improve overall functioning[38]. Allergic irritability syndrome is a brief, measurable approach to define the decreased ability to concentrate, bouts of irritability, and temper tantrums that occasionally occur as a complication of allergic rhinitis. We should consider the possibility of the presence of allergic and non-IgE hypersensitive conditions in any child or adult with autism who presents with irritability or increased aggressiveness, anxiety, inability to fall asleep or stay asleep, inability to concentrate, hyperactivity, and daytime fatigue[62]. It should be noted that commonly used allergy tests do not always detect allergy; therfore a comprehensive clinical history and physical examination are also important to assess the possibility of allergies or food intolerances[62]. Treatment of allergies can improve negative and challenging behaviours and lead to better overall functioning.

EMERGENCY ROOM AND OUTPATIENT GUIDELINES

Children with ASDs have a 30% higher risk of medical emergencies than their unaffected peers. This risk increases to 70% in teens between the ages of 15 and 18 years. The emergency department setting is in itself a real challenge for any clinician[63]. These settings become even more difficult when dealing with children with autism due to many barriers including communication and behavioural problems and anxiety. These children are also more vulnerable to inappropriate treatment[64,65]. Taken together these challenges can make the experience in the emergency room (ER) overwhelming and potentially traumatic for a child with autism and his or her family. Therefore, parents of children with autism should prepare a list of guidelines/concerns in advance with the support of the medical team[66]. At the same time, additional education and training of the emergency team and other hospital staff in dealing with children with ASD is needed. Table 2 showed the criteria of autism friendly Emergency Department. Improving staff knowledge, skills, approach, and confidence is the most important factor in minimizing the risk for inappropriate emergency management of children with ASD. Implementing patient- and family-centred care emerges as a priority for optimising ER care[67]. Environmental adaptations can have a direct impact on how comfortable children with ASD feel when they come to ER. These changes can be as small as ensuring the availability of calming objects, such as toys, books, activities, allowed snacks, and electronics such as iPads. Improvements could also include separate, quieter waiting areas with dim lighting for children with ASD where they can receive the attention they need while feeling safe and less anxious[68,69]. The outpatient setting should meet the necessary requirements for care coordination for children with autism with multiple waiting areas so that children can seclude themselves when they are anxious or fearful. It should be quiet with as little noise, dim lights, toys, and activities as possible to avoid agitating the children. Children should be explained and shown beforehand what the doctor will be doing. If a procedure is planned, such as a dental procedure, parents should

Table 2 Criteria of "Autism Friendly Emergency Department"

Staff
Available staff with additional training in autism management, and stakeholder engagement
Staff education includes awareness about sensory sensitivity, communication, and pain threshold, as well as how to interact with patients
Parenting with the experts
Minimizing the number of personnel to only the essential
Able to gain as much information as possible from both the patient and the caregiver
Facilities
Calming environment with offering calming objects like toys and iPads, or sending patients to separate, quieter waiting rooms and using dimmer lighting and noise control system
Special waiting room with calming toys and suitable TV shows
Short waiting time when possible
Available quiet examination room
Available admission questionnaire or checklist to help the physician discovered disorders that are difficult to be detected in children with autism
Well design exam room and treatment area to help motivate the children to stay in the room
Available sensory equipment to use such as ear defenders, sensory boxes filled with various sensory items, Picture Exchange Communication System cards, sensory toys (*e.g.*, squeezy balls), social stories, and communication aids
Available items to provide support, comfort, and security, including compression vests, blankets. and noise reduction earmuffs
Avoiding using sensory stimuli such as clutter, loud equipment, bright or fluorescent lighting
Parents
The use of one-page autism alert card or patient passport to provide emergency physicians with the needed information
Adequate partnership with parents
Family-centered care
The caregiver should be the guide to success
Medications and instruments
When choosing a medication, sensory issues such as taste or smell, textures, and temperature of treatment materials should be considered
The child should be exposed to and to touch all materials prior to using them if possible
The intervention can be modelled on the caregiver
Splints or bandages can be covered with non-threatening images

attend the appointment in advance[70].

CONCLUSION

Comorbidities are more common in children with ASDs than in the general population. Some genetic disorders are more common in children with ASD, such as FXS, DS, Duchenne muscular dystrophy, NF- type I, and TSC. Children with autism are more likely than the general population to have several neurological disorders. Sleep disorders are significant problems in individuals with autism, present in about 80% of them. GI problems are significantly more common in children with ASD, occurring in 46% to 84% of autistic children. Several categories of inborn errors of metabolism have been observed in some patients with autism including mitochondrial disorders, as well as other disorders. Some children with ASD have evidence of persistent neuroinflammation, altered inflammatory responses, and immune abnormalities. Anti-brain antibodies may play an important pathoplastic mechanism in autism. Allergic disorders are significantly more common in ASD and run through all age groups. The physician should rule out any medical concerns before moving on to other interventions or therapies. Children who enjoy good health have a better chance of learning. This can apply to all children, including those with autism.

ACKNOWLEDGEMENTS

The author thanks the anonymous reviewers who provide the manuscript with their valuable comments.

REFERENCES

1 **Isaksen J**, Bryn V, Diseth TH, Heiberg A, Schjølberg S, Skjeldal OH. Children with autism spectrum disorders - the importance of medical investigations. *Eur J Paediatr Neurol* 2013; **17**: 68-76 [PMID: 22954514 DOI: 10.1016/j.ejpn.2012.08.004]

2 **Carbone PS**, Farley M, Davis T. Primary care for children with autism. *Am Fam Physician* 2010; **81**: 453-460 [PMID: 20148499]

3 **Matson JL**, Nebel-Schwalm MS. Comorbid psychopathology with autism spectrum disorder in children: an overview. *Res Dev Disabil* 2007; **28**: 341-352 [PMID: 16765022 DOI: 10.1016/j.ridd.2005.12.004]

4 **Faras H**, Al Ateeqi N, Tidmarsh L. Autism spectrum disorders. *Ann Saudi Med* 2010; **30**: 295-300 [PMID: 20622347 DOI: 10.4103/0256-4947.65261]

5 **Summers J**, Shahrami A, Cali S, D'Mello C, Kako M, Palikucin-Reljin A, Savage M, Shaw O, Lunsky Y. Self-Injury in Autism Spectrum Disorder and Intellectual Disability: Exploring the Role of Reactivity to Pain and Sensory Input. *Brain Sci* 2017; **7** [PMID: 29072583 DOI: 10.3390/brainsci7110140]

6 **Devitt NM**, Gallagher L, Reilly RB. Autism Spectrum Disorder (ASD) and Fragile X Syndrome (FXS): Two Overlapping Disorders Reviewed through Electroencephalography-What Can be Interpreted from the Available Information? *Brain Sci* 2015; **5**: 92-117 [PMID: 25826237 DOI: 10.3390/brainsci5020092]

7 **Oxelgren UW**, Myrelid Å, Annerén G, Ekstam B, Göransson C, Holmbom A, Isaksson A, Åberg M, Gustafsson J, Fernell E. Prevalence of autism and attention-deficit-hyperactivity disorder in Down syndrome: a population-based study. *Dev Med Child Neurol* 2017; **59**: 276-283 [PMID: 27503703 DOI: 10.1111/dmcn.13217]

8 **Dube WV**, Farber RS, Mueller MR, Grant E, Lorin L, Deutsch CK. Stimulus Overselectivity in Autism, Down Syndrome, and Typical Development. *Am J Intellect Dev Disabil* 2016; **121**: 219-235 [PMID: 27119213 DOI: 10.1352/1944-7558-121.3.219]

9 **Langsdorff LC**, Domeniconi C, Schmidt A, Gomes CG, das Graças de Souza D. Learning by exclusion in individuals with autism and Down syndrome. *Psicol Reflex Crit* 2017; **30**: 9 [PMID: 32026984 DOI: 10.1186/s41155-017-0064-x]

10 **Lagan N**, Huggard D, Mc Grane F, Leahy TR, Franklin O, Roche E, Webb D, O' Marcaigh A, Cox D, El-Khuffash A, Greally P, Balfe J, Molloy EJ. Multiorgan involvement and management in children with Down syndrome. *Acta Paediatr* 2020; **109**: 1096-1111 [PMID: 31899550 DOI: 10.1111/apa.15153]

11 **Fujino H**, Saito T, Matsumura T, Shibata S, Iwata Y, Fujimura H, Imura O. Autism spectrum disorders are prevalent among patients with dystrophinopathies. *Neurol Sci* 2018; **39**: 1279-1282 [PMID: 29594829 DOI: 10.1007/s10072-018-3341-2]

12 **Parisi L**, Di Filippo T, Glorioso P, La Grutta S, Epifanio MS, Roccella M. Autism spectrum disorders in children affected by Duchenne muscular dystrophy. *Minerva Pediatr* 2018; **70**: 233-239 [PMID: 29795071 DOI: 10.23736/S0026-4946.16.04380-2]

13 **Garg S**, Lehtonen A, Huson SM, Emsley R, Trump D, Evans DG, Green J. Autism and other psychiatric comorbidity in neurofibromatosis type 1: evidence from a population-based study. *Dev Med Child Neurol* 2013; **55**: 139-145 [PMID: 23163236 DOI: 10.1111/dmcn.12043]

14 **Walsh KS**, Vélez JI, Kardel PG, Imas DM, Muenke M, Packer RJ, Castellanos FX, Acosta MT. Symptomatology of autism spectrum disorder in a population with neurofibromatosis type 1. *Dev Med Child Neurol* 2013; **55**: 131-138 [PMID: 23163951 DOI: 10.1111/dmcn.12038]

15 **Morotti H**, Mastel S, Keller K, Barnard RA, Hall T, O'Roak BJ, Fombonne E. Autism and attention-deficit/hyperactivity disorders and symptoms in children with neurofibromatosis type 1. *Dev Med Child Neurol* 2021; **63**: 226-232 [PMID: 32406525 DOI: 10.1111/dmcn.14558]

16 **Specchio N**, Pietrafusa N, Trivisano M, Moavero R, De Palma L, Ferretti A, Vigevano F, Curatolo P. Autism and Epilepsy in Patients With Tuberous Sclerosis Complex. *Front Neurol* 2020; **11**: 639 [PMID: 32849171 DOI: 10.3389/fneur.2020.00639]

17 **Mitchell R**, Barton S, Harvey AS, Williams K. Risk factors for the development of autism spectrum disorder in children with tuberous sclerosis complex: protocol for a systematic review. *Syst Rev* 2017; **6**: 49 [PMID: 28270230 DOI: 10.1186/s13643-017-0448-0]

18 **Pan PY**, Bölte S, Kaur P, Jamil S, Jonsson U. Neurological disorders in autism: A systematic review and meta-analysis. *Autism* 2020; 1362361320951370 [PMID: 32907344 DOI: 10.1177/1362361320951370]

19 **Pacheva I**, Ivanov I, Yordanova R, Gaberova K, Galabova F, Panova M, Petkova A, Timova E, Sotkova I. Epilepsy in Children with Autistic Spectrum Disorder. *Children (Basel)* 2019; **6** [PMID: 30691036 DOI: 10.3390/children6020015]

20 **Lamb GV**, Green RJ, Olorunju S. Tracking epilepsy and autism. *Egypt J Neurol Psychiatry*

Neurosurg 2019; **55**: 55 [DOI: 10.1186/s41983-019-0103-x]
21 **Saemundsen E**, Ludvigsson P, Rafnsson V. Autism spectrum disorders in children with a history of infantile spasms: a population-based study. *J Child Neurol* 2007; **22**: 1102-1107 [PMID: 17890408 DOI: 10.1177/0883073807306251]
22 **Samanta D**. An Updated Review of Tuberous Sclerosis Complex-Associated Autism Spectrum Disorder. *Pediatr Neurol* 2020; **109**: 4-11 [PMID: 32563542 DOI: 10.1016/j.pediatrneurol.2020.03.008]
23 **Lee BH**, Smith T, Paciorkowski AR. Autism spectrum disorder and epilepsy: Disorders with a shared biology. *Epilepsy Behav* 2015; **47**: 191-201 [PMID: 25900226 DOI: 10.1016/j.yebeh.2015.03.017]
24 **Talos DM**, Sun H, Zhou X, Fitzgerald EC, Jackson MC, Klein PM, Lan VJ, Joseph A, Jensen FE. The interaction between early life epilepsy and autistic-like behavioral consequences: a role for the mammalian target of rapamycin (mTOR) pathway. *PLoS One* 2012; **7**: e35885 [PMID: 22567115 DOI: 10.1371/journal.pone.0035885]
25 **Amiet C**, Gourfinkel-An I, Bouzamondo A, Tordjman S, Baulac M, Lechat P, Mottron L, Cohen D. Epilepsy in autism is associated with intellectual disability and gender: evidence from a meta-analysis. *Biol Psychiatry* 2008; **64**: 577-582 [PMID: 18565495 DOI: 10.1016/j.biopsych.2008.04.030]
26 **Besag FM**. Epilepsy in patients with autism: links, risks and treatment challenges. *Neuropsychiatr Dis Treat* 2018; **14**: 1-10 [PMID: 29296085 DOI: 10.2147/NDT.S120509]
27 **Depositario-Cabacar DF**, Zelleke TG. Treatment of epilepsy in children with developmental disabilities. *Dev Disabil Res Rev* 2010; **16**: 239-247 [PMID: 20981762 DOI: 10.1002/ddrr.116]
28 **Ming X**, Patel R, Kang V, Chokroverty S, Julu PO. Respiratory and autonomic dysfunction in children with autism spectrum disorders. *Brain Dev* 2016; **38**: 225-232 [PMID: 26235973 DOI: 10.1016/j.braindev.2015.07.003]
29 **Accardo PJ**, Barrow W. Toe walking in autism: further observations. *J Child Neurol* 2015; **30**: 606-609 [PMID: 24563477 DOI: 10.1177/0883073814521298]
30 **Richardson D**. Toilet training for children with autism. *Nurs Child Young People* 2016; **28**: 16-22 [PMID: 26954645 DOI: 10.7748/ncyp.28.2.16.s21]
31 **Kroeger K**, Sorensen R. A parent training model for toilet training children with autism. *J Intellect Disabil Res* 2010; **54**: 556-567 [PMID: 20576064 DOI: 10.1111/j.1365-2788.2010.01286.x]
32 **Matson JL**, Neal D, Hess JA, Kozlowski AM. Assessment of toileting difficulties in adults with intellectual disabilities: an examination using the profile of toileting issues (POTI). *Res Dev Disabil* 2011; **32**: 176-179 [PMID: 20940095 DOI: 10.1016/j.ridd.2010.09.014]
33 **Devnani PA**, Hegde AU. Autism and sleep disorders. *J Pediatr Neurosci* 2015; **10**: 304-307 [PMID: 26962332 DOI: 10.4103/1817-1745.174438]
34 **Souders MC**, Mason TB, Valladares O, Bucan M, Levy SE, Mandell DS, Weaver TE, Pinto-Martin J. Sleep behaviors and sleep quality in children with autism spectrum disorders. *Sleep* 2009; **32**: 1566-1578 [PMID: 20041592 DOI: 10.1093/sleep/32.12.1566]
35 **Klukowski M**, Wasilewska J, Lebensztejn D. Sleep and gastrointestinal disturbances in autism spectrum disorder in children. *Dev Period Med* 2015; **19**: 157-161 [PMID: 26384115]
36 **Yang XL**, Liang S, Zou MY, Sun CH, Han PP, Jiang XT, Xia W, Wu LJ. Are gastrointestinal and sleep problems associated with behavioral symptoms of autism spectrum disorder? *Psychiatry Res* 2018; **259**: 229-235 [PMID: 29091821 DOI: 10.1016/j.psychres.2017.10.040]
37 **Rzepecka H**, McKenzie K, McClure I, Murphy S. Sleep, anxiety and challenging behaviour in children with intellectual disability and/or autism spectrum disorder. *Res Dev Disabil* 2011; **32**: 2758-2766 [PMID: 21700417 DOI: 10.1016/j.ridd.2011.05.034]
38 **Xu G**, Snetselaar LG, Jing J, Liu B, Strathearn L, Bao W. Association of Food Allergy and Other Allergic Conditions With Autism Spectrum Disorder in Children. *JAMA Netw Open* 2018; **1**: e180279 [PMID: 30646068 DOI: 10.1001/jamanetworkopen.2018.0279]
39 **Bresnahan M**, Hornig M, Schultz AF, Gunnes N, Hirtz D, Lie KK, Magnus P, Reichborn-Kjennerud T, Roth C, Schjølberg S, Stoltenberg C, Surén P, Susser E, Lipkin WI. Association of maternal report of infant and toddler gastrointestinal symptoms with autism: evidence from a prospective birth cohort. *JAMA Psychiatry* 2015; **72**: 466-474 [PMID: 25806498 DOI: 10.1001/jamapsychiatry.2014.3034]
40 **Fulceri F**, Morelli M, Santocchi E, Cena H, Del Bianco T, Narzisi A, Calderoni S, Muratori F. Gastrointestinal symptoms and behavioral problems in preschoolers with Autism Spectrum Disorder. *Dig Liver Dis* 2016; **48**: 248-254 [PMID: 26748423 DOI: 10.1016/j.dld.2015.11.026]
41 **Wasilewska J**, Klukowski M. Gastrointestinal symptoms and autism spectrum disorder: links and risks - a possible new overlap syndrome. *Pediatric Health Med Ther* 2015; **6**: 153-166 [PMID: 29388597 DOI: 10.2147/PHMT.S85717]
42 **Prosperi M**, Santocchi E, Muratori F, Narducci C, Calderoni S, Tancredi R, Morales MA, Guiducci L. Vocal and motor behaviors as a possible expression of gastrointestinal problems in preschoolers with Autism Spectrum Disorder. *BMC Pediatr* 2019; **19**: 466 [PMID: 31779607 DOI: 10.1186/s12887-019-1841-8]
43 **Holingue C**, Newill C, Lee LC, Pasricha PJ, Daniele Fallin M. Gastrointestinal symptoms in autism spectrum disorder: A review of the literature on ascertainment and prevalence. *Autism Res* 2018; **11**: 24-36 [PMID: 28856868 DOI: 10.1002/aur.1854]
44 **Ajamian M**, Steer D, Rosella G, Gibson PR. Serum zonulin as a marker of intestinal mucosal barrier function: May not be what it seems. *PLoS One* 2019; **14**: e0210728 [PMID: 30640940 DOI: 10.1371/journal.pone.0210728]
45 **Coury DL**, Ashwood P, Fasano A, Fuchs G, Geraghty M, Kaul A, Mawe G, Patterson P, Jones NE.

Gastrointestinal conditions in children with autism spectrum disorder: developing a research agenda. *Pediatrics* 2012; **130** Suppl 2: S160-S168 [PMID: 23118247 DOI: 10.1542/peds.2012-0900N]

46 **Hampson DR**, Poduslo SE. Purification of proteolipid protein and production of specific antiserum. *J Neuroimmunol* 1986; **11**: 117-129 [PMID: 2419357 DOI: 10.1007/s10803-013-1973-x]

47 **Genuis SJ**, Bouchard TP. Celiac disease presenting as autism. *J Child Neurol* 2010; **25**: 114-119 [PMID: 19564647 DOI: 10.1177/0883073809336127]

48 **Rubenstein E**, Schieve L, Bradley C, DiGuiseppi C, Moody E, Thomas K, Daniels J. The prevalence of gluten free diet use among preschool children with autism spectrum disorder. *Autism Res* 2018; **11**: 185-193 [PMID: 29155492 DOI: 10.1002/aur.1896]

49 **Radzikowski A**, Wojnar M, Kulus M, Zalewski T. [Evaluation of the effect of gluten-free diet on nutritional status of children with florid celiac disease]. *Pediatr Pol* 1989; **64**: 150-154 [PMID: 2602046]

50 **Agana M**, Frueh J, Kamboj M, Patel DR, Kanungo S. Common metabolic disorder (inborn errors of metabolism) concerns in primary care practice. *Ann Transl Med* 2018; **6**: 469 [PMID: 30740400 DOI: 10.21037/atm.2018.12.34]

51 **Cheng N**, Rho JM, Masino SA. Metabolic Dysfunction Underlying Autism Spectrum Disorder and Potential Treatment Approaches. *Front Mol Neurosci* 2017; **10**: 34 [PMID: 28270747 DOI: 10.3389/fnmol.2017.00034]

52 **Schrieken M**, Visser J, Oosterling I, van Steijn D, Bons D, Draaisma J, van der Gaag RJ, Buitelaar J, Donders R, Rommelse N. Head circumference and height abnormalities in autism revisited: the role of pre- and perinatal risk factors. *Eur Child Adolesc Psychiatry* 2013; **22**: 35-43 [PMID: 22923066 DOI: 10.1007/s00787-012-0318-1]

53 **Bridgemohan C**, Cochran DM, Howe YJ, Pawlowski K, Zimmerman AW, Anderson GM, Choueiri R, Sices L, Miller KJ, Ultmann M, Helt J, Forbes PW, Farfel L, Brewster SJ, Frazier JA, Neumeyer AM. Investigating Potential Biomarkers in Autism Spectrum Disorder. *Front Integr Neurosci* 2019; **13**: 31 [PMID: 31427932 DOI: 10.3389/fnint.2019.00031]

54 **Yektaş Ç**, Alpay M, Tufan AE. Comparison of serum B12, folate and homocysteine concentrations in children with autism spectrum disorder or attention deficit hyperactivity disorder and healthy controls. *Neuropsychiatr Dis Treat* 2019; **15**: 2213-2219 [PMID: 31496704 DOI: 10.2147/NDT.S212361]

55 **Rossignol DA**, Frye RE. Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. *Mol Psychiatry* 2012; **17**: 290-314 [PMID: 21263444 DOI: 10.1038/mp.2010.136]

56 **Gladysz D**, Krzywdzińska A, Hozyasz KK. Immune Abnormalities in Autism Spectrum Disorder-Could They Hold Promise for Causative Treatment? *Mol Neurobiol* 2018; **55**: 6387-6435 [PMID: 29307081 DOI: 10.1007/s12035-017-0822-x]

57 **Meltzer A**, Van de Water J. The Role of the Immune System in Autism Spectrum Disorder. *Neuropsychopharmacology* 2017; **42**: 284-298 [PMID: 27534269 DOI: 10.1038/npp.2016.158]

58 **Connery K**, Tippett M, Delhey LM, Rose S, Slattery JC, Kahler SG, Hahn J, Kruger U, Cunningham MW, Shimasaki C, Frye RE. Intravenous immunoglobulin for the treatment of autoimmune encephalopathy in children with autism. *Transl Psychiatry* 2018; **8**: 148 [PMID: 30097568 DOI: 10.1038/s41398-018-0214-7]

59 **Zimmerman AW**, Connors SL, Matteson KJ, Lee LC, Singer HS, Castaneda JA, Pearce DA. Maternal antibrain antibodies in autism. *Brain Behav Immun* 2007; **21**: 351-357 [PMID: 17029701 DOI: 10.1016/j.bbi.2006.08.005]

60 **Mostafa GA**, El-Sherif DF, Al-Ayadhi LY. Systemic auto-antibodies in children with autism. *J Neuroimmunol* 2014; **272**: 94-98 [PMID: 24837704 DOI: 10.1016/j.jneuroim.2014.04.011]

61 **Jyonouchi H**. Autism spectrum disorders and allergy: observation from a pediatric allergy/immunology clinic. *Expert Rev Clin Immunol* 2010; **6**: 397-411 [PMID: 20441426 DOI: 10.1586/eci.10.18]

62 **Klein GL**, Ziering RW, Girsh LS, Miller MF. The allergic irritability syndrome: four case reports and a position statement from the Neuroallergy Committee of the American College of Allergy. *Ann Allergy* 1985; **55**: 22-24 [PMID: 2409849]

63 **Iannuzzi DA**, Cheng ER, Broder-Fingert S, Bauman ML. Brief report: Emergency department utilization by individuals with autism. *J Autism Dev Disord* 2015; **45**: 1096-1102 [PMID: 25261249 DOI: 10.1007/s10803-014-2251-2]

64 **Cohen-Silver JH**, Muskat B, Ratnapalan S. Autism in the emergency department. *Clin Pediatr (Phila)* 2014; **53**: 1134-1138 [PMID: 25031320 DOI: 10.1177/0009922814540983]

65 **Liu G**, Pearl AM, Kong L, Brown SL, Ba D, Leslie DL, Murray MJ. Risk Factors for Emergency Department Utilization Among Adolescents with Autism Spectrum Disorder. *J Autism Dev Disord* 2019; **49**: 4455-4467 [PMID: 31414259 DOI: 10.1007/s10803-019-04166-y]

66 **Normandin PA**, Coffey KA, Benotti SA, Doherty DP. Autism Emergency Care Success: Plan, Collaborate, and Accommodate. *J Emerg Nurs* 2018; **44**: 662-664 [PMID: 30415737 DOI: 10.1016/j.jen.2018.07.013]

67 **Nicholas DB**, Muskat B, Zwaigenbaum L, Greenblatt A, Ratnapalan S, Kilmer C, Craig W, Roberts W, Cohen-Silver J, Newton A, Sharon R. Patient- and Family-Centered Care in the Emergency Department for Children With Autism. *Pediatrics* 2020; **145**: S93-S98 [PMID: 32238535 DOI: 10.1542/peds.2019-1895L]

68 **Samet D**, Luterman S. See-Hear-Feel-Speak: A Protocol for Improving Outcomes in Emergency Department Interactions With Patients With Autism Spectrum Disorder. *Pediatr Emerg Care* 2019;

35: 157-159 [PMID: 30702545 DOI: 10.1097/PEC.0000000000001734]

69 **Wood EB**, Halverson A, Harrison G, Rosenkranz A. Creating a Sensory-Friendly Pediatric Emergency Department. *J Emerg Nurs* 2019; **45**: 415-424 [PMID: 30679010 DOI: 10.1016/j.jen.2018.12.002]

70 **Singh V**, Pinkett-Davis M, Kalb LG, Azad G, Neely J, Landa R. A preliminary study of care coordination services within a specialized outpatient setting for youth with autism spectrum disorder. *Int J Care Coord* 2019; **22**: 109-116 [DOI: 10.1177/2053434519893659]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com