

CO-MORBID MEDICAL CONDITIONS IN AUTISM SPECTRUM DISORDERS

Vladimir Trajkovski

University "Ss. Cyril and Methodius", Faculty of Philosophy, Institute of Special Education and Rehabilitation, Skopje, Republic of Macedonia

Abstract

Introduction: many children and adults with autism spectrum disorder (ASD) have comorbid medical conditions. Recent large-scale studies have confirmed that several medical conditions are significantly more prevalent in people with autism compared to the typical population. Comorbid conditions may be markers for basic psychopathology and may require a more varied treatment approaches. Comorbid conditions in ASD are: anxiety disorders, bipolar disorder, gastrointestinal disorders, depression and other psychopathological disorders, ADHD, Fragile X syndrome, mental retardation, neuroinflammation and immune disorders, nonverbal learning disorder, motor clumsiness, obsessive-compulsive disorder, Tourette syndrome, epilepsy, sensory problems, tuberous sclerosis, oxidative stress, acquired mitochondrial dysfunction and metabolic abnormalities, etc.

Methodology: the main goal of the article is to present the most frequent medical conditions in ASD in a sample from the Republic of Macedonia. The main task of the research is to show that accurate diagnosis and treatment often results in an improved level of functioning and decreased severity of symptoms. This is a retrospective, descriptive study where 102 medical records from the Macedonian Scientific Society for Autism were analyzed. In the study, 88 males and 14 females were included with a mean age of 6.9 ± 3.63 years.

The results: the most prevalent medical conditions were acute infectious disease (40%): varicella in 35 (34%) and measles in 7 (6%) of the persons with autism. Angina was seen in 34 (33%) persons of the sample. Sixteen patients met the criteria for any kind of allergies on food, medicaments, and inhalants. Convulsions, as a symptom, were represented in 15 (14%) of the subjects. Eleven patients had lower respiratory tract infections such as bronchitis and bronchopneumonia. Eleven percents had gastrointestinal disorders. Genetic disorders were not detected.

Conclusion: medical comorbid and consecutive pathological processes can have a negative impact on behavior, socialization, communication, cognitive function and sensory processing of individuals with autism. The failure to identify medical conditions, in part, is due to communication impairments and ambiguous symptomatology, but under-diagnosis also exists. Many of these medical conditions are treatable, and often resulting in improved quality of life for the patient and the family. Accurate identification and solving the conditions of medical comorbid with autism will help the reduction of the immense emotional, physical and financial burden of the families and the guardians.

Key words: autism, comorbid, medical, conditions, Republic of Macedonia

Introduction

Autism is defined as a neurodevelopmental disorder, characterized by repetitive behaviors, social withdrawal, and communication deficits (Gillberg and Coleman, 2000). The term “co-morbid condition” is commonly used to describe associated medical and developmental disorders. This term implies a condition that is distinct from the disorder itself, which may not be true for many conditions associated with an ASD.

It is also recognized as the second most common developmental disability after mental retardation, among children (Centers for Disease Control and Prevention, 2009). Many children and adults with a diagnosis of autism spectrum disorder (ASD) have comorbid health problems. Studies from the USA, Europe and Asia that carried out detailed clinical investigations confirmed that medical comorbidities were highly prevalent in children and adolescents diagnosed with ASD (Gurney, McPheeters & Davis 2006). 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”** (Kose et al., 2013). Comorbid conditions may be markers for underlying pathophysiology and request a more varied treatment approach. Developmental, psychiatric, and neurologic disorders frequently co-occur in children with autism spectrum disorders (ASDs) and may have a significant impact on the identification,

treatment needs, functional status, and progress of children with ASD (Gillberg & Billstedt, 2000).

Autism occurs predominantly in males, with a male:female ratio of 4 to 1. There is also an increased prevalence in African-Americans. The occurrence of autism varies among nations, and it increases in most countries (Currenti, 2010).

In the clinical and psychological literature, children with ASD are often described as having one or more of a variety of medical and psychological comorbidities, including higher than expected rates of mental retardation, epilepsy, gastrointestinal disorders, attention-deficit/hyperactivity disorder (ADHD), depression, anxiety disorders, sleep disorders, bipolar disorder, Fragile X syndrome, neuroinflammation and immune disorders, nonverbal learning disorder, motor clumsiness, obsessive-compulsive disorder, Tourette syndrome, sensory problems, tuberous sclerosis, oxidative stress, acquired mitochondrial dysfunction and metabolic abnormalities (Gurney, McPheeters & Davis 2006).

Method

The main goal of the article is to present the most frequent medical conditions in ASD in the sample from the Republic of Macedonia. Main task of the research is to show that accurate diagnosis and treatment often results in improved level of functioning and decreased severity of symptoms. This is a retrospective, descriptive study where 102 medical records from the Macedonian Scientific Society for Autism were analyzed. Autism was diagnosed with ICD-10 and DSM-IV criteria. As measures of health care use, parents were first asked whether during the past 12 months their child saw a doctor, nurse, or other health professional.

In the study, 88 males and 14 females were included. The mean age of participants was 6.9 ± 3.63 years. The survey includes questions about sociodemographics, physical and mental health status of children and socioeconomic status of parents. Interviews with parents of children with autism spectrum disorders were conducted in Macedonian language in the period from January 2000 through January 2013. Obtained data were stored in statistical program SPSS for Windows version 17. Statistical analysis was made by descriptive statistical measure such as: mean, standard deviation, and percentages.

Results

This is a first study with complete analysis of autism in the Republic of Macedonia, which has shown that in the Centers for social welfare and in the Medical centers; sometimes the data for children with autism are inconvenient. In this study, 102 persons were analyzed, from which two were monozygotic female siblings and one person was dizygotic male sibling. Male:female ratio was 6,28:1. The minimal age of participants was 3 years while the maximal age was 20 years. The results from this survey of children's health suggest a consistent pattern of substantially higher health care needs and use among children with autism, relative to other children.

In the sample the most prevalent medical condition were acute infectious disease (41%) varicella in 35 (34.5%) and measles in 7 (6.5%) of the persons with autism. Neonatal jaundice was seen in 40 children with ASD (39%). Angina was comorbid condition in 34 (33%) persons of the sample. Sixteen patients met criteria for some kind of allergies on food, medicaments, and inhalants. Convulsions as a symptom were represented in 15 (14%) of subjects. Eleven patients had lower respiratory tract infections such as bronchitis and bronchopneumonia. 11% had gastrointestinal disorders (constipation and diarrhea). Six parents referred hernia to their children. Autism was associated with eye disorders in four examinees (hypermetropia, strabismus and nystagmus). Middle ear infections also were detected in four children which is less than 4%. Only two patients with ASD had infection with *Candida albicans* (Table 1).

Table 1. *Co-morbid medical conditions in persons with ASD*

Co-morbid medical condition	N	%
Acute infectious disease	42	41
Neonatal jaundice	40	39.2
Angina	34	33.3
Allergy	16	15.7
Convulsions	15	14.7
Gastrointestinal disorders	12	11.8
Hernia	6	5.9
Eye disorders	4	3.9
Middle ear infections	4	3.9
Candidiasis	2	1.9

The findings reported in this paper showed an important pattern of parent rates of concurrent conditions and needs from health care system. In this study, 204 parents of persons with ASD were examined for medical conditions. The most frequent were neuropsychiatric disorders seen in 6.9% of this cohort. Parents had dementia, epilepsy, neurosis, Parkinson syndrome and schizophrenia as well. Anamnesis data showed that 10 parents (4.9%) had speech delay or some kind of speech disorder in their childhood. Seven parents (3.4%) had significant signs of autoimmune disorder such as Hashimoto thyroiditis, Sjögren syndrome, psoriasis, vitiligo, systemic lupus erythematosus. Mental retardation, hypertension and malignant tumors were presented in four parents (2%) respectively. Three parents (1.5%) in this group gave positive answers for diabetes mellitus.

Table 2. *Medical conditions in parents of persons with ASD*

Medical condition	N	%
Neuropsychiatric disorders	14	6.9
Speech disorders	10	4.9
Autoimmune disorders	7	3.4

Allergies	5	2.4
Mental retardation	4	2
Carcinoma	4	2
Hypertension	4	2
Diabetes mellitus	3	1.5

Discussion

Current neurological, immunological, metabolic, endocrinological, and epidemiological research is at the leading edge of a paradigm shift in our understanding of ASD. While autism has been commonly assumed to be a neurodevelopment and behavioral disorder, and kept within the boundaries of psychiatry and neurology, it is now increasingly recognized as a whole-body disorder, with the core deficits in communication, social interaction, restrictive/stereotypic behaviors, and other commonly seen behaviors that have been attributed to ASD, being surface manifestations of a systemic and complex disease process. These findings support previous research that autism spectrum disorder commonly co-occurs with other developmental, psychiatric, neurologic, autoimmune, and sensory disorders.

There is solid evidence of immune dysfunction in individuals with autism. Results of numerous studies point to abnormal immune function, including ongoing 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., 2005; 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 behavioral and cognitive impairments. Persons with ASD in our sample were not vaccinated consistently. Due to this reason there is frequent prevalence of acute infectious diseases. Individuals with autism often display immune abnormalities in the form of altered cytokine profiles, autoantibodies, changes in immune cell function and abnormal mast cell activation (Trajkovski et al., 2004; Molloy et al., 2006; Ashwood et al., 2011; Theoharides et al., 2012).

Accumulating evidence suggests an association between exposure to neonatal jaundice and autistic disorders, as well as other disorders of psychological development. The excess risk of developing a disorder in the spectrum of psychological development disorders after exposure to jaundice as a neonate was between 56% and 88% (Maimburg et al., 2010). In our study neonatal jaundice was detected in 39.2% and it could play some role in the pathogenesis of autism.

Children with autism frequently have recurrent early infections consistent with *Streptococcus* existing in biofilm state in the ears and sinuses, which can travel through the stomach to the small intestine, where it could establish a biofilm state in the duodenum (Cosford, 2009). Pediatric Autoimmune Neuropsychiatric Disorder Associated with *Streptococcus*, also known as PANDAS, is a condition that can occur within a child with a diagnosis of ADHD, autism, Asperger's syndrome, obsessive compulsive disorder, or tic disorder (such as Tourettes syndrome). PANDAS leads to autoimmune-mediated inflammation of the brain, and usually occurs after several bouts of Strep throat, but may manifest even if the parent cannot recall a history of *Streptococcal* infection in their child (Murphy & Pichichero, 2002). Our study group showed that one third of persons with ASD had tonsillopharyngitis which is relatively big percentage. Tonsil and adenoid removal in cases of PANDAS is needed and the clinical features of autism will improve. Also, we should fight against infection with *Streptococcus*, to avoid alterations in diet and nutrition, together with using probiotic supplementation.

Food and inhalant allergies, including frank atopic diseases and food intolerances are common in autism (Schieve et al., 2012). It has been demonstrated that a challenge with nasal allergens results in increase of autism symptoms in over half of the studied children (Boris and Goldblatt, 2004) while treatment of allergies often results in improvement in behaviors such as anxiety, hyperactivity, and irritability, commonly attributed to "being autistic" (Chen et al., 2013).

In previous study we examined specific IgA, IgG, and IgE antibodies to food antigens in 35 participants with autistic disorder and 21 of their siblings. Statistically significant higher plasma concentration of IgA antibodies against alpha-lactalbumin, beta-lactoglobulin, casein, and gliadin were found in children with autistic disorder. Plasma concentrations of IgG antibodies against alpha-lactalbumin, beta-lactoglobulin, and casein in participants with autistic disorder were significantly higher. IgE-specific antibodies (alpha-lactalbumin, beta-lactoglobulin, casein, and gluten) as well as plasma concentration of total IgE were also statistically significantly higher in the

participants with autistic disorder (Trajkovski et al., 2008). Both IgE and non-IgE mediated allergic reactions are increasingly recognized causative factors of anxiety and mood disorders. Also, these allergic reactions contribute to difficulty in focusing, irritability, tics, daytime fatigue and sleep problems in both children and adults. In this survey, it was found that approximately 16% of autistic persons suffer from some kind of allergy on food, inhalants, etc. These findings indicate intestinal immunological disturbances and the need for gluten-casein free diet in this population.

Health professionals should be aware that when a child or adult with autism presents '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 (Theoharides et al., 2012).

Epilepsy in autism is not uncommon. The prevalence of epilepsy found in autistic children is up to 10 times higher compared to general pediatric population (30% vs. 2-3%). Autism and epilepsy co-occur in some genetic disorders that follow a Mendelian pattern of inheritance. These disorders may therefore share a common neurochemical substrate that is targeted by the psychotropic mechanism of action of several antiepileptic drugs (Saengpatracha, 2011). In contrast to this study our anamnestic data showed convulsions in less than half ASD people or in 15%. Probably it is due to the not advanced technique used in the diagnosis of epilepsy.

When epileptiform activity is present in the ASD 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 behaviors, in addition to reducing seizure activity (Muñoz-Yunta et al., 2008).

Gastrointestinal problems are a commonly found in autism and may be related to problem behaviors, sensory overresponsivity, deregulated sleep, anxiety and irritability (Chandler et al., 2013). Over the past several years there has been an increased recognition of gastrointestinal comorbidities among individuals with autism, including increased intestinal permeability, diarrhea, constipation, gastro esophageal reflux, digestive enzyme deficiency and bacterial dysbiosis (Wasilewska et al., 2009). Other digestive symptoms include abdominal pain, pyrosis (heartburn), chronic diarrhea, flatulence, drooling or excessive salivation, vomiting, regurgitations, weight loss, rumination, bruxism (teeth grinding), irritability. Diarrhea and constipation are common, and constipation can coexist with episodes of diarrhea. In the case of diarrhea, the stools are semi-liquid, very fetid with mucus and undigested food; sometimes they can have a sandy/grainy consistency and other times show blood. In

our study diarrhea and constipation were most frequent gastrointestinal disorders. The Macedonian sample showed less than 12% gastrointestinal problems from which diarrhea and constipation were most prevalent.

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 (Williams et al., 2012).

Increasingly, ASD or ASD-like characteristics have been described in individuals with a range of different genetic syndromes including: Tuberous Sclerosis Complex, Fragile X, Cornelia de Lange, Down, Angelman, Coffin-Lowry, Cohen Laurence-Moon-Biedel, Marinesco-Sjogren, Moebius, Rett and William's syndromes. The strength of association or co-occurrence between a given genetic syndrome and ASD is variable, with prevalence estimates ranging from 5% in individuals with Down syndrome to 60% in individuals with Tuberous Sclerosis Complex (Moss and Howlin, 2009). In our cohort there was no any case of secondary autism which is underestimated result due to low resolution cytogenetic and molecular techniques. Also, our physicians don't think about association of autism and genetic disorders. The effectiveness of ASD specific interventions for use in individuals with genetic syndromes who show ASD or ASD-like characteristics is not known. It is likely that a combination of ASD specific interventions and targeted interventions which focus on specific areas of difficulty will be appropriate. However, further research is required to evaluate such approaches.

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.

Conclusion

Autism has become a worldwide concern, and is a very common neurodevelopmental disorder among children. It has become a very prevalent disorder among

children within a short period of time. Persons identified with autism spectrum disorder had high frequencies of one or more co-occurring non-ASD developmental, psychiatric, neurologic, metabolic, immune, gastrointestinal and possibly causative medical diagnoses.

Medical co-morbidity and consecutive pathological processes can negatively impact behavior, socialization, communication, cognitive function and sensory processing of individuals with autism. The failure to identify medical conditions is due in part to communication impairments and ambiguous symptomatology, but there is also under-diagnosis. Many of these medical conditions are treatable, often resulting in improved quality of life for the patient and family. Correct identifying and addressing medical co-morbidity in autism will help in reducing the immense emotional, physical and financial burden on families and carers. Some of these conditions appeared to cluster and have important implications for delay in identification or diagnosis of ASD and the complexity of intervention for children with ASD and co-occurring disorders. These data highlight the need for clinicians to keep in mind the high prevalence of associated diagnoses with an ASD diagnosis, and the possibility that in younger children other symptoms or disorders may be masking or obscuring core symptoms of ASD, which would lead to a diagnosis.

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

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КОМОРБИДНИ МЕДИЦИНСКИ СОСТОЈБИ КАЈ АУТИСТИЧЕН СПЕКТАР НА НАРУШУВАЊА

Владимир Трајковски

*Универзитет „Св. Кирил и Методиј“, Филозофски факултет,
Институт за дефектологија, Скопје, РМ*

Апстракт

Вовед: Многу деца и возрасни со аутистичен спектар на нарушувања (АСН) имаат коморбидни медицински состојби. Последните големи студии потврдиле дека неколку медицински состојби се значително поприсутни кај лицата со аутизам во споредба со типичната популација. Коморбидните состојби можат да бидат маркери за основната патофизиологија и да побараат повеќе различни пристапи во третманот. Коморбидни состојби кај АСН се: анксиозни растројства, биполарно растројство, гастроинтестинални нарушувања, депресија и други психопатолошки нарушувања, АДХД, фрагилен X-синдром, интелектуална попреченост, невроинфламација и имунолошки нарушувања, нарушувања во невербалното учење, моторна несмасност, опсесивно-компулсивно нарушување, Туретов синдром, епилепсија, сензорни проблеми, туберозна склероза,

оксидативен стрес, стекната митохондријална дисфункција и метаболички абнормалности итн.

Методологија: Главна цел на трудот е да се презентираат најчестите медицински состојби кај АСН во примерок од Република Македонија. Главната задача на истражувањето е да се покаже дека точната дијагноза и третманот често резултираат со подобро ниво на функционирање и намалување на тежината на симптомите. Ова е ретроспектива, дескриптивна студија со којашто беа анализирани 102 медицински досиеја од Македонското научно здружение за аутизам. Во студијата беа вклучени 88 машки и 14 женски индивидуи со просечна возраст $6,9 \pm 3,63$ години.

Резултати: Најраспространети медицински состојби беа акутните инфективни заболувања (40%), и тоа: варичела кај 35 (34%) и мали сипаници кај 7 (6%) од лицата со аутизам. Ангина беше видена кај 34 (33%) лица од примерокот. Шеснаесет пациенти ги исполнија критериумите за некој вид алергии на храна, лекови и инхаланти. Конвулзии како симптом, беа застапени кај 15 (14%) од испитаниците. Единаесет пациенти имале инфекции на долниот респираторен тракт, како што се бронхитис и бронхопневмонија. Единаесет проценти имале гастроинтестинални нарушувања. Генетски нарушувања не беа откриени.

Заклучок: Медицинските коморбидитети и последователните патолошки процеси можат негативно да влијаат на однесувањето, социјализацијата, комуникацијата, когнитивната функција и на сензорната обработка на лица со аутизам. Неуспехот да се идентификуваат медицински состојби се должи делумно на комуникациското нарушување и двосмислената симптоматологија, но постои и потпроцентото дијагностицирање. Многу од овие медицински состојби можат да се лекуваат, што често резултира со подобрен квалитет на животот на пациентот и на семејството. Правилно идентификување и решавање на медицинските коморбидни состојби кај аутизмот ќе помогне да се намали огромната емотивна, физичка и финансиска загриженост на семејствата и негувателите.

Клучни зборови: аутизам, коморбидитет, медицински, состојби, Република Македонија