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The review of most frequently occurring medical disorders related to aetiology of autism and the methods of treatment

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The medical understanding of autism has changed since it was first defined by Kanner. Nowadays medicine identifies many medical abnormalities and diseases, which may underline or aggravate the cognitive aspect, behavioural issues and general health in autists. This includes chronic inflammation of gastrointestinal tract, dysbiosis, maldigestion, malabsorption, malnutrition, food intolerance, allergies, chronic viral, fungal and bacterial infections, impaired kidney function, impaired detoxification of endo- and exotoxins, disorders of metal ion transportation. Treatment of the above mentioned conditions combined with improving detoxification mechanisms, followed by a special diet and individually customized supplementation of nutritional deficiencies may lead to the improvement of the functioning of these patients, changing their level of functioning and self-dependence.

The aim of this paper is to present medical problems of children with autism which may be identified and treated by general practitioners as a review of current medical papers related to Autism Spectrum Disorder, in the context of author's professional experience, based on the medical cases from author's practice.

Key words : autism, autism treatment, ammonia, dysbiosis, hepatic encephalopathy, gastrointestinal tract, multiple sclerosis, uric acid

Autism is a developmental disorder (Filipek et al. 1999). The initial symptoms can often be observed in early stages of childhood. The most common symptoms of autism are disruptions of social interactions, worsened communication skills, repetitive and ritualistic behaviours, self-stimulation, tantrums and sometimes aggression. (Johnson et al. 2007).

According to the most recent statistics from the Centres for Disease Control, USA nearly 1 in 150 children born today have or will eventually have autism (Cone 2009).

The social and economic impact of this disease can be really unpredictable, as it impacts the ability to conduct an independent life.

The majority of children with autism are socially or psychiatrically handicapped throughout their life. The costs of supporting children with ASDs in the UK were estimated to be £ 2.7 billion each year (Knapp et al. 2009).

The medical understanding of autism has changed since it was first defined by Kanner. Leo Kanner published his first paper identifying autistic children back in 1943, asserting he had noticed such children since 1938. In his work he focused on psychological and behavioural aspects of this disease rather than on the investigations of possible medical issues underlying developmental regression of these children.

Kanner believed that autism has the neuropsychological cause, and therefore he created the "refrigerator mother theory" (Kanner 1956). This view, further propounded by Professor Bruno Bettelhem in his book "The empty fortress: infantile autism and the birth of the self" (1967), which claimed that the traumatized unloved child retreated into autism, was so widely accepted by medical profession, that most researchers and clinicians did not look for "medical" answers to autism because they believed it was a disorder that was medically untreatable. Even nowadays children labelled

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with autism are usually not undergoing further medical investigation, as this condition is still perceived as psychological by many medical doctors.

The first major attack on Bettelheim's theory was conducted by Bernand Rimland, father of an autistic son, psychologist and founder of Autism Research Institute. Rimland was the first authoritative voice to dispute Bettelheim's research and call into question his conclusions. He published his book "Infantile autism: the syndrome and its implications for a neural theory of behavior" in 1964.

Since then the Autism Research Institute established in 1967 by Rimland has contributed a lot to the research in the field of biomedical symptoms underlying autism spectrum disorder. The first studies focused on thrimerosal toxicity and autism, but soon the independent scientists and researchers movement started to come out with new findings and new ideas focusing on medical aspects of autism.

Nowadays science already identifies many biological disorders associated with this disease, which might play a role of etiological factors or can aggravate this condition. The researchers are identifying in autistic children numerous medical problems. Most prominent of them seem to be gastrointestinal tract pathologies, including dysbiosis, inflammatory bowel syndrome, pancreatic exocrine insufficiency, celiac disease, maldigestion, malabsorption, food intolerance, and food allergies, leading to vitamin deficiencies and malnutrition (Horvath and Perman 2002). Immune system deficiencies occur in majority of autistic patients investigated to date. Chronic inflammation seems to play very important role in aggravating their conditions.

Patients with autism frequently have disorders of main biochemical pathways of the organism, including methylation, transsulphation, oxidative stress, lactic acidosis. These conditions are often explained by impaired ability to detoxify and toxic exposure to most common environmental toxins as pesticides, heavy metals, xenotoxins and difficulties in detoxifying of endotoxins like ammonia, arabinitol, propionic acid. Many researchers have identified in autistic patients numerous disorders of metabolism of neurotransmitters, including serotonin, dopamine, catecholamines etc. Also, disorders of metal ion transportation and electrolytes are discussed, especially in the context of thimerosal toxicity studies (Aschner et al. 2006, Palmer et al. 2006, 2009). It is already generally agreed that this disease is multifactoral and the behavioural picture of autism may be caused by different medical issues. Although the genetic factor seems to play very important role both in autism epidemiology and in vulnerability to the environmental factors, like heavy metal toxicity, it is not the aim of this paper to present the current genetic theories of autism.

The aim of this paper is to present the medical conditions, which require proper diagnosis and treatment, and which are aggravating health problems of children with autism and seem to influence their behaviour. Many of these medical issues are related to the pathology of gastrointestinal system, which seems to be seriously contributing to autism.

Paul Shattock at the Autism Research Unit investigated the theory that autism is a consequence of a metabolic disorder, whereby certain biologically active peptides and other related compounds (derived mainly but not exclusively from dietary gluten and/or casein) are not metabolised correctly in the autists (Whiteley and Shattock 2002). His theory led to widespread use of gluten- and casein-free diet as a medical intervention in treating autistic syndrome (Christison and Ivany 2006). This intervention is rated by parents of autistic children as one of most effective, according to Autism Research Institute. The gluten- and casein-free diet for autistic children is even more justified by immunological findings, revealing increased immune response to dietary peptides in autistic subjects (Vojdani et al. 2004a, b).

In 1999 Andrew Wakefield published in the Lancet his study, in which he reported bowel symptoms in a prospective case of twelve consecutive vaccinated children diagnosed with autism spectrum disorders and other disabilities, and alleged a possible connection with the MMR vaccination (Wakefield 1999). Wakefield has described the endoscopic findings in 12 children diagnosed with autism, revealing nodular hyperplasia, mucosal abnormalities, including non-specific inflammation. Although very controversial, this study draw a lot of public attention into the gut pathology as a possible underlying cause of the autistic behaviour, resulting in new studies, carried out by different authors. The attempts to prove or disapprove Wakefield's discovery resulted in further findings, which are indicating a strong link between autism and gastrointestinal symptoms and gastrointestinal pathologies. Horvath at al have performed endoscopies on the group of 36 non-verbal autistic children, revealing by histological examination the evidence of grade I or

II reflux esophagitis in 25 (69.4%), chronic gastritis in 15, and chronic duodenitis in 24 patients as well as low carbohydrate digestive enzymes and increased pancreato-biliary secretion after administering of secretine (Horvath et al. 1999). The other studies (Kugathasan 2001) are linking autism to inflammatory bowel disease of autoimmune origin. Also, the dysbiosis (Parracho et al. 2005) seems to play an important role in this pathology, increasing autoimmune processes by the increased immune response to Clostridial antigens (Finegold et al. 2002, Song et al. 2004).

Hence, the treatment with oral vancomycin and other non-absorbable antibiotics and antifungals is proposed to relieve both gastrointestinal symptoms and helps cognitive functions as well (Sandler et al. 2000). Oral vancomycin is perceived as immunomodulating antibiotic and its safety and efficacy was proven even in a long-term treatment in children with non-related to autism gastrointestinal autoimmune diseases, like primary sclerosing cholangitis (Davies et al. 2008). The other non-absorbable antibiotics, like neomycin and gentamycin (well known in the treatment of hepatic encephalitis), or a new non-absorbable antibacterial agent rifaximin may be also useful in the treatment of the bowel inflammation associated with a severe dysbiosis in autistic patients, along with other antibiotic treatment (Whelan 2000).

Since many of these children have problems with a chronic constipation (Afzal et al. 2003), which may be partially caused by paralysis of the peristaltic movements by the bacterial toxins, this treatment should be associated with the regulation of bowel movements by lactulose or macrogols. The low uric acid level is a common finding in autistic children in the author's practice. Since no studies of low uric acid levels in autistic patients were published to date, author made a review of the significance of this marker in other chronic diseases. There is a strong evidence of neuroprotective role of uric acid against oxidative stress caused by peroxynitrite and hypouricemia has a strong association with multiple sclerosis. Also, hypouricemia is often related to AIDS and might be a prognostic symptom in this condition. This is not a purpose of this paper to introduce a new medical hypothesis, but in author's opinion hypouricemia in autistic patients requires further investigations.

Since dramatic case of Hannah Poling (Poling et al. 2006), 9-year-old autistic child whose preexisting mitochondrial disorder was aggravated by her vaccines has drawn the attention of the researchers to the possible mitochondrial dysfunction in autistic patients, there is many ongoing research activity in this field. The mitochondrial disease are difficult to investigate and this diagnosis is not in the competence of general practitioners, however, the symptoms and a family history should be always taken into consideration and followed by proper investigations by specialists in the field (Holtzman 2008, Rossignol and Bradstreet 2008, Weissman et al. 2008). The diagnosis of mitochondrial disease is very complex. There are nevertheless some parameters, like lactic acid and ammonia, which should be checked in the serum of autistic children, especially if they had unexplained episodes of vomiting, drowsiness or drug-resistant epileptic-like seizures.

Some cases of autistic children seem to present transient or permanent hyperammonemia (Cohen 2006) which should be in each case differentiated with urea cycle disorder (Görker and Tüzün 2005), but also may result from carnitine deficiency (Filipek et al. 2004) or mitochondrial dysfunction (Clark-Taylor and Clark-Taylor 2004). Since the ammonia is known as a dangerous neurotoxin, an elevated blood ammonia level, although it may be secondary, must never be ignored. The question why ureagenic capacity of some of the autistic children is not sufficient must be always diagnosed individually. Hyperammonemia is well recognised as a main cause of hepatic encephalitis and elevated ammonia levels itself may explain behavioural and cognitive changes and some of neurotransmitter disregulation observed in autism (Cohen 2006). Therefore, in children with hyperammonemia, the proper medical control of chronic constipation and dysbiosis is a vital part of the medical approach, as it is a well proven treatment for ammonia-induced hepatic encephalitis and helps to decrease ammonia production in the gut. The recommended treatment for hyperammonemia should also include sodium benzoate and arginine supplementation. Unfortunately, sodium benzoate is not easy available in some European countries, so this pharmacological option is not easy to implement. The efficacy of the enzymatic system in the liver is crucial for the detoxification of ammonia and other endo-and egzotoxins, therefore the support of the liver function by multivitamin supplementation, sylimaryne and ornithine aspartate is a very important part of the treatment protocol.

One proposed aetiology for autism is viral infection on a very early developmental stage. This mechanism

may work either through the direct infection of the central nervous system or through alteration of the immune response of the mother or offspring, or through a combination of these. Some hypotheses are linking autism to viral infection, especially caused by measles virus and human herpes viruses (Singh et al. 1998, Nicolson et al. 2007). Gillberg describes two cases of autism linked to encephalitis caused by herpes virus and autism. The first is the case of 14 years old girl, who developed autism after the episode of herpes virus encephalitis (Gillberg 1986), another is the case of a previously healthy man who contracted herpes encephalitis at the age of 31 years, and over the following months developed all the symptoms considered diagnostic of autism (Gillberg 1991). This case reports cast doubt on the notion of autism as an exclusively developmental disorder. It is suggested that temporal lobe damage may cause autism in some cases. Similar observations had Ghaziuddin (Ghaziuddin et al. 2002) describing autistic symptoms following herpes encephalitis. The role of the viral factor in autism remains unclear, but the studies reported above draw the attention to underlying viral infections in autistic children, which may become active due to their immune system deficiencies and may aggravate the symptoms, either directly, by causing inflammation in central nervous system, or by causing cross-immunity or autoimmunity against the host nervous tissues (Plioplys et al. 1989, Vojdani et al. 2002, 2003).

According to everyday practice of the author, autistic symptoms may improve if the patients are provided with the individualised treatment of their medical problems underlying Autism Spectrum Disorder. The author never attempted to treat the autism *per se*, as this diagnosis is in the author's perception rather psychological then medical in nature. Notwithstanding the fact that every person who has been diagnosed with autism has the same right to proper medical diagnosis and treatment as anyone else, does not necessarily receive the adequate care. The difficulty is that these patients are frequently nonverbal, always have the problems with communication and their sensation of pain is frequently altered, so they are not able to express their ailments. The further difficulty is the blood drawing as these patients are much more reluctant to allow this happen to them. This applies to all the medical procedures in this group of patients, as often even the proper physical examination might be a challenging task for the doctor. Nevertheless, despite all the difficulties described above we are not allowed to refuse treatment only and solely on the grounds of their autistic diagnosis. Each case of autism requires profound medical insight to diagnose possible metabolic, infectious or immune disease or toxic exposure in order to better identify the underlying cause and implement early medical intervention. The medical intervention should be individualized.

The picture of structural and biochemical changes of autistic spectrum disorder remains still unclear and requires further investigation, nevertheless, current scientific findings tend to define autism as a disease affecting the brain rather than the "disease of the brain". Since the behavioural and psychological signs of autism are unhelpful in medical diagnostic efforts, each patient with autism should undergo in-depth laboratory investigation, including biochemistry and haematology, assessment of the liver and kidney function, immune system assessment including auto antibodies, total immunoglobulin, ASLOT and viral screens, as well as investigating bacteriology cultures from stool and assessment of inflammatory parameters in gastrointestinal tract. This should lead to an improvement in functioning of affected children and help them to obtain possibly highest grade of self-dependence.

The question arises, if society can afford performing expensive medical investigations on the autistic children. In this place we should rather ask a different question - can society afford failing of the diagnosis and treatment of these patients. Each case of an autistic child improving after a medical intervention is important for the society. Improving the ability of these patients to lead relatively independent existence has a great economic impact.

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