Rocz Panstw Zakl Hig 2013;64(1):1-12

HOW NUTRITIONAL STATUS, DIET AND DIETARY SUPPLEMENTS CAN AFFECT AUTISM. A REVIEW

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ABSTRACT

Autism is a neurodevelopmental disorder with symptoms arising that are apparent throughout the patient's lifespan. Autism Spectrum Disorders (ASD) are characterised by impaired social and communication interactions as well as restricted, repetitive interests and behaviour. Currently in Poland, about 50 000 people suffer from autism, of which 1/5 are children. Epidemiological studies show that the incidence of autism is increasing, which may be due to the diagnostic category of ASD having been developed. Of vital importance in the treatment of autism, is early diagnosis which is conducive to more rapidly improving the quality of patients' health.

It is believed that both genetic and environmental factors may affect the development of the disease. Moreover, expert opinion emphasises the importance of making an adequate diagnosis when the first symptoms of autism start appearing which can be both psychological, gastro-intestinal and metabolic ones. Conventional treatment is based on the combination of behavioural and dietary therapy together with pharmacotherapy. For example, adapting an appropriate diet could help alleviate the disease severity, as well as the psychological and gastrointestinal symptoms. Much scientific research has indicated that pathogenesis of autism may have a beginning already in foetal life. During pregnancy, specialists should take special heed of metabolic disorders, which can increase the risk of ASD in children. One of the dietician's tasks are to properly assess the nutritional status of mothers before and during pregnancy, thereby allowing changes in nutrition to be made wherever necessary in order that metabolic indicators be improved.

Thus an important part of autism therapy is the improving patient's nutritional status to prevent the onset of gastrointestinal symptoms. Adopting diets and tailored to individual disease symptoms, is linked to the nutritional requirements and food preferences of the patient. Specialists also emphasise that continual monitoring of the diet and nutritional status of children with ASD is required. It is also essential to start adequate dietary management in autistic patients with overweight, obesity or wasting, caused by improper nutrition. Frequently only a dietary therapy is insufficient to effectively treat autism. Many studies demonstrate the need to supplement the nutritional deficiencies of autistic patients with fatty acids *omega*-3, probiotics, vitamins and minerals in combination with medical and psychological interventions. A properly designed elimination diet adapted to the patient's individual may also lead to relief of the autism symptoms and the occurrence of gastrointestinal disorders. Parents and caregivers should therefore be aware of the benefits of nutritional therapy and need for proper monitoring the treatment of patients with ASD. A review of nutritional factors, dietary treatments and diet supplementation in patients with ASD is presented.

Keywords: *autism, developmental disorders, diet, nutritional status, diet supplementation*

STRESZCZENIE

Autyzm to zaburzenia o podłożu neurorozwojowym, trwające przez całe życie pacjenta. Charakterystycznymi objawami są nieprawidłowości w zachowaniu, obejmujące zaburzenia w strefach rozumowania, kontaktów socjalnych i porozumiewania się. Obecnie w Polsce żyje około 50 tysięcy osób dotkniętych autyzmem, w tym 1/5 stanowią dzieci. Wyniki badań epidemiologicznych dowodzą, iż częstość występowania autyzmu stale wzrasta, co może być spowodowane poszerzeniem diagnostyki ASD (ang. *Autism Spectrum Disorders*). Podstawowe znaczenie w terapii autyzmu ma wczesne rozpoznanie choroby, sprzyjające szybszej poprawie stanu zdrowia pacjentów.

Na rozwój autyzmu mają wpływ zarówno czynniki genetyczne, jak i środowiskowe. Specjaliści podkreślają znaczenie odpowiedniej diagnostyki pierwszych objawów autyzmu, zarówno psychicznych jak i trawienno-metabolicznych. W leczeniu autyzmu wykorzystywane są różne kierunki terapii: leczenie farmakologiczne, behawioralne lub dietetyczne. Odpowiednie dostosowanie diety do stanu zaawansowania choroby może mieć pozytywne skutki w wyciszaniu i łagodzeniu objawów psychicznych i gastroenterologicznych autyzmu.

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Autorzy licznych doniesień naukowych wskazują, iż patogeneza autyzmu może mieć początek już w życiu płodowym dziecka. Należy zwrócić uwagę na występowanie zaburzeń metabolicznych u kobiet w czasie ciąży, które mogą zwiększać ryzyko występowania zaburzeń autystycznych u dziecka. Zadaniem dietetyka jest odpowiednia ocena stanu odżywienia matki przed i w czasie ciąży, pozwalająca na wprowadzenie zmian w żywieniu, prowadzących do poprawy wskaźników metabolicznych. Poprawa stanu odżywienia pacjenta przy jednoczesnym niedopuszczeniu do pojawienia się objawów ze strony układu pokarmowego jest istotnym elementem terapii autyzmu. Odpowiednie dostosowanie diety do indywidualnych objawów choroby wiąże się z uwzględnieniem potrzeb i preferencji żywieniowych pacjenta. Autorzy wielu prac wskazują na potrzebę dokładniejszego monitorowania sposobu żywienia i stanu odżywienia dzieci z ASD. Istotne jest podjęcie odpowiedniego leczenia dietetycznego u pacjentów z nadwagą, otyłością lub wyniszczeniem, spowodowane nieprawidłowym żywieniem. Dietoterapia nie jest wystarczająca przy wspomaganiu leczenia autyzmu. Lekarze i dietetycy w celu uzupełnienia niedoborów pokarmowych pacjentów decydują się na połączenie leczenia farmakologicznego, psychologicznego i dietetycznego z terapią suplementami kwasów tłuszczowych, probiotyków, witamin i składników mineralnych.

Właściwie skomponowana dieta eliminacyjna uwzględniająca indywidualne potrzeby pacjenta może prowadzić do złagodzenia objawów autyzmu oraz występowania zaburzeń żołądkowo-jelitowych. Rodzice i opiekunowie powinni mieć świadomość korzyści wynikających z dietoterapii i potrzeby monitorowania jej w leczeniu pacjentów z ASD.

W artykule przedstawiono przegląd wybranych, udokumentowanych badań i doniesień naukowych dotyczących leczenia dietetycznego objawów zaburzeń ze spektrum autyzmu.

Słowa kluczowe: *autyzm, zaburzenia rozwoju, dieta, stan odżywienia, suplementacja diety*

INTRODUCTION

Autism Spectrum Disorders (ASD) are characterised by a complex of serious neurodevelopmental disorders, classified as symptoms of the Pervasive Developmental Disorders group (PDD). The disease often becomes manifest in the first three years of life [23]. It is characterised by a marked impairment in social interaction, delayed employment of language and restricted patterns of behaviour; termed as a triad of behavioural impairments. In addition, autistic children frequently display serious behavioural disturbances, such as aggression, tantrums and self-injurious behaviour [17, 36].

The prevalence of ASD is increasing worldwide. It is estimated that at least 10-20 per 10 thousand infants are born annually with autism [11]. In 1998, autism was diagnosed on average in 1/250 USA children, whilst for 2007 in 1/150 children [16, 75]. The disease occurs four times more frequently amongst boys (4:1), whereas in girls, the symptoms can be more intensified [70]. In Poland, there are currently about 50 000 people with autism, of which 1/5 are children [6].

It is presumed that the disease is caused by the interaction of both genetic and environmental factors [73]. Development of autism may also have important links to metabolic disorders of gastrointestinal system [25]. Incomplete digestion of dietary gluten and casein in the lumen of the small intestine and increased absorption of incompletely hydrolysed peptides may impair the nervous system. These peptides may demonstrate biological activity similar to endogenous opioid peptides [13, 14, 78]. Patients with autism may also suffer from leaky gut syndrome, which is caused by damage to the intestinal mucosa, inflammation and abnormal bacterial overgrowth leading to a disorder of bowel motility [40, 57, 86]. Other symptoms include hypochlorhydria of the gastric juice (low gastric acid secretion), and decreased activity of disaccharidases in the intestinal juice [37].

In autistic children, *Kushak* et al. [53] conducted about 500 gastroscopies and biopsies, showing that chronic inflammation of the digestive tract was prevalent, including oesophagitis, gastritis and enteritis inflammation. In 55% of the children, decreased levels of disaccharidases and glucoamylase were observed together with lactase and sucrose, thus predisposing towards disorders associated with starch metabolism, carbohydrate malabsorption and intestinal disorders. Additionally, other untoward gastrointestinal symptoms were observed such as abdominal pain, gas, bloating, chronic diarrhoea, loose stools, allergies and food intolerance.

Such an extensive array of symptoms in the digestive tract in patients with ASD, strongly suggests the need for introducing nutritional therapy in addition to routine treatment. Adequate nutrition can lead to relief of symptoms, both digestive and metabolic as well as psychological ones. Unfortunately, still very few doctors and nutrition experts monitor the diet and nutrition of autistic patients.

MATERNAL METABOLIC DISORDERS AND THE RISK OF AUTISM

Numerous reports indicate that the pathogenesis of autism already originates during the prenatal life of the child [19, 41, 55]. Neurological and behavioural dysfunctions, characteristic of ASD, may be associated with maternal metabolic abnormalities occurring before and during pregnancy [20].

In a case-controlled study, *Krakowiak* et al. [51] evaluated whether the incidence of metabolic disorders during pregnancy, (such as: diabetes, hypertension and obesity) is associated with the prevalence of autism risk in children. It was concluded that this risk and other developmental disorders could increase if the mother is obese or suffers from type 2 diabetes. It was found that the incidence of the latter and gestational diabetes was higher in mothers who bore a child with ASD (9.3% vs. 6.4%). Furthermore, the incidence of hypertension and obesity were respectively higher in mothers of children with ASD compared to normal (3.7% vs. 1.3% and 21.5% vs. 14.3%). Metabolic abnormalities were also more common in women whose offspring suffered from ASD, compared with controls (28.6% vs. 19.4%). The results of the study may therefore indicate a relationship between metabolic abnormalities arising before and during pregnancy and the more frequent incidence of autism.

Gardener et al. [31] conducted a meta-analysis on epidemiological studies that indicated the coexistence between maternal metabolic abnormalities and the development of autism. Taking into account 50 prenatal factors including diabetes and hypertension, the authors demonstrated that complications in pregnancy may increase the risk of autism in the offspring.

NUTRITIONAL STATUS ASSESSMENT AND FOOD PREFERENCES OF CHILDREN WITH ASD

In 2009, the USA *Conference of Gastroenterology* formed a consensus on the monitoring of intestinal disorders in patients with ASD [5]. It was agreed that paediatricians are obliged to perform routine monitoring of anthropometry as part of assessing nutritional status of children with ASD.

As well as developing obesity, patients with ASD demonstrate a malnutrition risk due to inadequate energy intake from the diet and the problems caused by improper absorption of nutrients from the intestines as well as indigestion. Any deviation from a normal nutritional status, (ie. overweight, obesity, cachexia), in patients with ASD should thus be a signal to the specialist for instigating dietary treatment [5].

Studies that have assessed dietary and nutritional status of autistic children found that every child was underweight, despite an adequate intake of energy with the diet; the children's daily food rations containing inadequate amounts of dietary fibre, calcium, potassium, iron, and vitamin D [74].

A study by *Herdon* et al. [35] analysed the macro- and micronutrients supplied by different food groups in ASD diagnosed children (n=46), which was compared to (n=31), typically healthy developing children. ASD children were found to consume significantly more vitamin B_6 and vitamin E than controls and less dairy products; this being associated with a body calcium deficiency. These differences have likewise been reported in children on the GF-CF diet (gluten free and casein free diet). A significant amount of children in both groups did not fulfil the intake recommendations for dietary fibre, calcium, iron and vitamin D.

Levy et al. [56] assessed the influence of individual nutrients in the diet of 62 children with ASD in order to determine whether gastrointestinal disorders in ASD patients are associated with the type of food consumption. The results were compared with standard RDA levels (recommended dietary allowance), in relation to energy, protein, carbohydrates and fats. Findings showed that dietary energy, carbohydrate and fat intake were at the recommended level, whilst average dietary protein intakes exceeded the RDA (211%, range: 67-436%). These patients also exhibited negative symptoms of the gastrointestinal system such as diarrhoea and constipation. The need to describe the relationship between the intake of certain nutrients and the occurrence of gastrointestinal problems was stressed, as was the fact that an important therapeutic element for treating autism is the use of a selective diet.

Ho and *Eaves* [38] analysed differences related to nutritional status and diet of Canadian children, aged on average 13.3 years, with ASD, assessing the contribution of different dietary nutrients where individual food intake was determined by a three day food record. The diet composition was made in consultation with parents and health-carers of the ASD children and the analysis included the intakes of energy, minerals, vitamins, carbohydrates, proteins and fats. The results were then compared to RNI recommendations, (reference nutrient intakes), for the Canadian population. Protein intakes for these children matched those recommended, whereas dietary intakes of carbohydrates and fats were too high compared to healthy children; 42.6% of the examined children were obese of whom almost half demonstrated low physical activity levels. The study showed that obesity may be correlated with increased symptoms of autism.

The aim of a study by *Curtin* et al. [18] study was to assess the prevalence of obesity in children and adolescents with ASD, (n=85 272 children aged 3-17 years). Data were gathered through telephone interviews with parents and carers of ASD children and used for the NSCH survey, (National Survey of Children's Health). It was found that more children were obese with ASD than healthy ones (30.4% vs. 23.6%), and it was concluded that additional research is required to better understand factors affecting the development of obesity in this population grouping.

Eating habits and dietary intake of nutrients in autistic children, (n=19 versus n=15 normally developing controls), were also analysed by *Johnson* et al. [44]. The results showed behavioural differences between the two groups however there were no significant differences in the nutritional status. Similar results were obtained by *Schreck* et al. [77], indicating significant behavioural problems associated with dietary preferences and food intake of autistic children. The latter also showed an adequate intake of fruits and vegetables, dairy products and starch compared to the control group.

INCIDENCE OF GASTROINTESTINAL SYMPTOMS IN PATIENTS WITH ASD

Until recently, autism, along with other developmental disabilities, was regarded as a central nervous system disease. The medical research community has ignored the various other disorders coexisting with the autism, such as dysfunction of the gastrointestinal and immunological systems. As a result, patients were treated only by psychiatrists and therapists, and so long-term gastrointestinal problems arose, which often became permanent during the patient's lifetime [5].

Dysfunction of the gastrointestinal system is more common in ASD children compared with those properly developing. Another problem is the diagnosis of symptoms, because most autistic children are not able inform their parents and/or carers about discomforts caused by gastrointestinal disorders. The Autism Treatment Network (ATN) indicate that gastrointestinal disorders like diarrhoea or constipation, occur nearly in half of ASD children and their incidence increases with age [52].

A study conducted by *Horvath* et al. [39], assessed the structure and function of the upper gastrointestinal tract in autistic patients with gastrointestinal symptoms. The most common symptoms observed were diarrhoea, constipation and flatulence. ASD children, (69.4%), demonstrated oesophageal reflux, gastritis and duodenal inflammation. In addition 58.3% of the ASD children possessed enzyme abnormalities affecting carbohydrate digestion, but there were no irregularities in pancreatic function. It was concluded that gastroesophageal reflux disease and disturbances in disaccharide malabsorption may contribute to disorders of the patients' development.

Afzal et al. [3] evaluated the incidence of constipation in ASD children associated with gastrointestinal dysfunction. A moderate or severe occurrence of constipation in 36% of children with ASD was observed compared to a control group (9%). Another study by *Ibrahim* et al. [42] determined whether patients with autism had increased risks of gastrointestinal symptoms compared with controls; a higher incidence of constipation (33.9% vs 17.6%) and problems with nutrition and feeding (24.5% vs 16.1%), was respectively seen in children with ASD. It was also found that neurobehavioral problems can cause gastrointestinal disorders.

A further study, *Kazek* et al. [48], assessed the incidence of gastrointestinal disorders in ASD patients who had reported gastrointestinal symptoms; all examined patients presented with indications for endoscopy of the upper gastrointestinal tract. Those well-nourished were 60% and malnourished were 17%; 23% were overweight or obese. Abdominal chronic pain was reported in 80% of patients with ASD. Histopathological analysis showed inflammatory changes in the duodenum and nonspecific colitis in 70% of examined patients. It was concluded that gastrointestinal disorders may predispose to intensifying behavioural disorders in autistic patients.

In contrast, a case-controlled study by *Black* et al. [8], for assessing gastrological disorders in ASD children, did not find any evidence that autistic children suffer more often from gastrointestinal dysfunction, compared to healthy children. This was performed by assessing their medical history for the prevalence and intensities of chronic gastrointestinal inflammation, celiac disease, food intolerance and gastrointestinal symptoms.

In all, appropriate nutritional status assessment and dietary treatment of the gastrointestinal symptoms can bring major benefits to the treatment of autism. Doctors and nutritionists should regularly discuss with parents and carers of autistic children about symptoms of gastrointestinal disorders and include them in the therapeutic strategy.

DIETARY THERAPY

It is very important to make dietary adjustments when treating autism as well as on how best diets may be consumed. An appropriate dietary intervention allows for quick relief of the disease symptoms and should be complementary to pharmacotherapy and behavioural therapy. Reducing intake of certain food products and dishes is associated with reduced incidence of numerous disorders of the gastrointestinal symptoms in patients, such as: inflammatory bowel disease, food intolerance and allergies, infections, together with biological and viral infections.

Elimination diets

These are based on reducing or completely removing those foods from the diet that adversely affect patients with ASD; most frequently, they are the ones causing the food intolerances or allergies. This exclusion must also include removal of any substances added to

foods that are found to be allergenic. Because of the potential hazards of malnutrition, these elimination diets should be supervised by a physician and/or nutritionist. In a study by *Trajkovski* et al. [79], some autistic patients showed excessive amounts of IgG, IgE and IgA antibody classes in response to allergenic substances contained in foodstuffs. It has been shown that immune dysregulation (e.g. presence of IgE) may occur in ASD children whose consequences are the classic allergic response. However, after adopting an elimination diet, the adverse clinical symptoms observed in the study subjects had improved.

A typical strategy is to therefore eliminate those nutrients from the diet that may constitute a real risk of allergy or food intolerance. Very often, a GF-CF diet, (gluten-free and casein-free diet), forms the starting point towards dietary treatment of autistic patients. A GF-CF diet consists in completely removing those products which are the main source of gluten as well as those with trace amounts.

The diet should also eliminate casein which is the main protein ingredient of cow's milk and all dairy products. Complete removal of dietary milk/dairy products leads however to calcium insufficiency, which is the main source of the building blocks of bones and teeth in a child's diet. Fortunately, there are various alternatives such as products made from goat's or sheep's milk that have similar compositions to cow's milk although they could also be a source of new allergens. For this reason specialists usually recommend soy or rice milk; yeast flakes with added molasses can be a substitute for cheese [32].

A randomised trial from Denmark named '*ScanBrit*' [87], determined the impact of the GF-CF diet on social behaviour in children with ASD through dietary analysis after 12 months. Child behaviour were rated according to the ADOS scale (Autism Diagnostic Observation Schedule), GARS (*Gilliam* Autism Rating Scale) and VABS (*Vineland* Adaptive Behaviour Scales). It was suggested that that appropriate dietary intervention can have a significant impact on the psychosocial development of patients. A study by *Elder* et al. [24] also looked at the health impact that a GF-CF diet has on ASD child patients, (n=15 aged 2 to 16 years). Results for disease symptoms were however statistically inconclusive although the parents reported an improvement of child behaviour, after 3 months of dieting.

In a study by *Knivsberg* et al. [49], on autistic children, dietary elimination of gluten and casein through the GF-CF diet showed much better improvements in child development compared to a control group. The impact of removing dietary gluten and casein products on autistic children were also determined by *Cornish* [14] where a 3-day dietary record was made by parents filling in a questionnaire; children on the GF-CF diet showed some deficiencies of zinc, calcium, iron, vitamin A, vitamin B12 and riboflavin compared to those not on this diet. Fruit and vegetable intake was however higher in the former whereas bread and potato consumption was lower in children who were on the GF-CF diet. In terms of child behaviour, *Seung* et al. [78] reported no significant differences of children on a GF-CF diet for 6 weeks, however it was emphasised that measuring the effectiveness of diet requires a longer time frame. Other numerous studies support the hypothesis that the GF-CF diet may have legitimate use in the patients undergoing ASD treatment but despite its high suitability, patients may require further improvements and diet modifications that are tailored to individual patient needs.

One of the main causes of emotional problems in children can be incorrect diet, chiefly related to the consumption of food products containing dyes, artificial flavours and preservatives. Food products containing chemical substances added during manufacturing processes may also cause allergies or intolerance and have carcinogenic or mutagenic effects [60].

The *Feingold* Diet, (a food restriction diet), is often used for treating autism symptoms. Its primary recommendation is to remove dye additives and preservatives from foodstuffs of the daily meal and is based on eliminating all products containing harmful substances, food additives and flavour enhancers. This includes salicylate which can be found in aspirin, some toothpaste, lotions, mouthwash, cough syrups, chewing gum as well as natural foodstuffs such as apples, grapes, cucumbers, oranges and bananas [29].

The ketogenic diet

This is a high-fat, low-protein and low-carbohydrate diet used to treat children with refractory epilepsy [63]. The classic ketogenic diet provides about 90% of the energy from fat; the remaining being from proteins and carbohydrates. The diet should be used for 2-3 years after an initial period of fasting, when urinary ketone concentration reaches required levels. During the diet, the body is in the state of ketosis where a metabolic shift occurs from using glucose, to the main source of energy being ketone compounds formed from fatty acids in the blood [66].

A study from 2003 suggests that the ketogenic diet may alleviate the symptoms of ASD where the effect of this diet after 6 months was determined in 30 autistic children aged 4-10 years. A significant improvement in social and communication abilities was thence observed in 18 cases. Significant effects of the diet were observed in 2 patients. In contrast, severe symptoms of autism were observed in children who were not on the ketogenic diet. Complications such as low birth weight or selenium deficiency did not occur. It was suggested

that the ketogenic diet can be used as a therapy to treat symptoms of autism [26].

Studies by *Canitano* et al. [12] looked at prevalence of epilepsy in children with autism where in 1/3 of autistic children aged 2-3 years, epileptiform symptoms may occur. From this, it was hypothesised that that a ketogenic diet may have positive impact on the mechanisms of neurological diseases. Nonetheless, it should be emphasised that adopting the ketogenic diet therapy requires extensive experience from both the doctor and dietician. During the dietary treatment, patients should have the concentration of ketone bodies in blood serum controlled; if not, then there is a high risk of a number of metabolic disorders occurring.

The specific carbohydrate diet (SCD)

This was first introduced and described by *Gottschall* [33], as one of the methods for autism treatment. Its purpose is to alleviate symptoms of malabsorption and prevent growth of pathogenic intestinal microflora. The diet mainly recommends monosaccharides, whose sources are fruit, some vegetables and honey whereas the consumption of complex carbohydrates are restricted. Polysaccharides take much longer to digest than monosaccharides and, being thus abnormally, (asymmetrically), distributed in the gastrointestinal tract, may lead to difficulties of absorption where residual food becomes a breeding ground for pathogenic intestinal flora. Yeast overgrowth and bacteria can cause intestinal dysbiosis, (intestinal catarrh), with the formation of bacterial and fungal products as well as excessive production of intestinal mucus [10, 30]. The main aim of this diet is to restore normal function of the intestine and to prevent the development of intestinal pathogenic microorganisms. Recommended constituents are meat, eggs, natural cheeses, homemade yogurt, vegetables (cabbage, cauliflower, onions, spinach, peppers), fresh fruit, nuts (almonds, brazil nuts, walnuts), soaked lentils and beans [33].

Low oxalate diet

In gastro-intestinal system dysfunction, certain substances, like oxalates, may impair the child's neurological development and cause abnormalities in the nervous system [56]. Although autism is a genetic disease, some metabolic disorders may contribute to intensifying the clinical symptoms, including high concentrations of oxalate in the blood serum. In ASD patients, *Konstantinowicz* et al. [50] demonstrated 3-fold higher concentrations of plasma oxalate, compared with recommended values (5.6 mmol/l vs 1.84 mmol/l) and 2.5 times higher oxalate levels in urine. Higher concentrations of oxalate in blood serum and urine may thus be one of the reasons of ASD pathogenesis.

Foodstuffs especially rich in the oxalates are spinach, beetroots, cocoa, black tea, figs, lemon zest, green apples, black grapes, kiwis, tangerines, strawberries, berries, oats, wheat, millet, peanuts, cashew nuts , hazelnuts, almonds and blueberries [58].

The Acceptable Daily Intake (ADI) of dietary oxalate in an adult is 250 mg/day. The daily intake of oxalate in a typical western diet can however be up to 1000 mg/day. Patients with autism should therefore limit intake of foodstuffs rich in oxalate to 40-50 mg/day [72]. During the Low Oxalate Diet therapy, patients should receive supportive supplements as appropriate, like arginine, taurine, vitamins A and E, glucosamine, glutathione, thiamine, magnesium, CoA, citrate, magnesium, calcium and zinc.

DIETARY SUPPLEMENTS

The *Pauling* theory [64] states that mental disorders can arise from various disruptions in the body such as from biochemical reactions, genetic factors, diet and deficiencies of vitamins and/or minerals.

Supplements used to treat autism should however, neither provoke nor aggravate the symptoms of autism. Supplements should also be given after a recovery is made from poor digestion and intestinal dysbiosis which is being treated with an appropriate nutritional therapy. Indeed, supplements such as fatty acids *omega-3*, probiotics, vitamin B_6 with magnesium, vitamins: C, A, D, B_{12}, folic acid, iron and bioelements have been shown to ameliorate some of the symptoms of autism.

Omega-3 fatty acids

A deficiency or an insufficient intake of omega-3 fatty acids can cause abnormal development of the nervous system in childhood, resulting in loss of concentration, hyperactivity, dyslexia, dyspraxia and the autistic disorder [80].

A pilot study [4] was conducted to assess whether taking omega-3 improves behaviour or can mitigate some of the other symptoms of autism. Subjects were 22 autistic children, aged 5-17 years who were investigated for 6 weeks during which a supplement containing EPA and DHA and vitamin E was taken in doses of 1.5 g/day; the control group having not taken the supplement however vitamin E was consumed. It was seen that *omega-3* significantly improved speech and articulation in those children taking this supplement and that there was a greater openness in relations with other people as compared to controls. In contrast, a study of *omega-3* supplementation in adult patients with ASD by *Politi* et al. [67] demonstrated no significant improvement of disease severity and frequency, both in patients during the administration of supplements as well as when the

6 weeks of supplement *omega-3* therapy had finished; NB. the supplement had contained both 0.93 g EPA and DHA and 5 mg of vitamin E in order to avoid excessive oxidation of lipids. Concluding then, there was in fact no change seen in the mental disorders of adults with severe autism following the supplementation.

The effect of taking an EPA supplement was also tested by a case study made on a boy with ASD, *Johnson* and *Hollander* [45], to see if the severe symptoms of ASD could be alleviated. The patient suffered from serious psychiatric symptoms such as tantrums, aggression, depression, anxiety or obsessive thoughts. Over 4 weeks, the EPA dose was progressively increased and then for 8 weeks the patient was administered with 540 mg EPA / day. After the therapy had finished, specialists and parents noted behavioural improvements that included the elimination of excessive fear and excitement. It was concluded though, that more comprehensive clinical studies are required for assessing the merits of the omega-3 fatty acids supplementation to treat the symptoms of autism.

Probiotics

Microorganisms with specific probiotic properties are able to increase the body's utilization of food ingredients and vitamin synthesis together with inhibiting the development of certain pathogens and having various immunomodulatory effects [85].

In the USA, according to specialists opinion, almost 1/5 doctors administer probiotics supplements as a form of autism treatment. Due to the frequent occurrence of gastrointestinal dysfunction in patients with ASD, ie. constipation, acute diarrhoea, inflammatory intestinal disease, irritable bowel syndrome (IBS), the use of probiotics may be an indication for adjuvant therapy. Probiotics may therefore exert a beneficial effect on the restoration and maintenance of intestinal microflora balance and rebuilding and restoring the intestinal mucosal protective function of intestinal epithelial cells [16].

Vitamin B_6 and magnesium

Vitamin B_6 is involved in the synthesis of neurotransmitters such as serotonin, aminobutyric acid (GABA), dopamine (DA), norepinephrine (NE) and epinephrine (E) and ASD patients may exhibit abnormal biochemical synthesis of these neurotransmitters. Deficiencies of minerals and vitamins may also be associated with abnormal intestinal function and damaged immune systems. *Martineau* et al. [59] treated ASD children with dietary vitamin B_6 and magnesium supplements and observed significantly improved behaviour compared to those not taking the supplementation. Another study, *Wong* and *Smith* [88], however showed no effect in ASD child patients receiving CAM therapy (complementary and alternative medical therapy), having proper diets introduced or dietary supplementation; no significant benefits of vitamin B_6 and magnesium supplementation were demonstrated.

The influence of vitamin B_6 supplementation on changes in the behaviour of autistic children was also studied by *Rimland* et al. [71] and was one of the first to focus on clinical use of vitamin B_6 supplementation in the treatment of autism. Notwithstanding that both the authors and parents witnessed behavioural improvements, the numerous methodological ambiguities of the analysis prevented any definitive conclusions from being drawn. *Adams* et al. [1] evaluated total plasma vitamin B_6 in ASD children and found that they had 75% higher levels than in the control group. The study also observed low activities of pyridoxal kinase and pyridoxal-5-phosphate (PLP) in the ASD children. It is known that a low conversion of pyridoxal to PLP, (which is an active cofactor and substrate for the synthesis of several key neurotransmitters), can cause neurobehavioral disorders in autism.

Adams and *Holloway* [2] studied the effect of established vitamin B_6 doses on the symptoms of ASD, and autistic children had significantly increased levels of this vitamin in the blood (75% higher) compared to controls. High concentrations of vitamin B_6 are associated with low activity of kinase and oxidase enzymes which transform different forms of vitamin B_6 to the active pyridoxal-5-phosphate form. It was concluded that there is a functional need for administering high doses of vitamin B_6 when treating ASD symptoms.

Vitamin C

Vitamin C is essential for many biochemical processes involved in the synthesis of neurotransmitters and also has antioxidant properties for protecting the body against free radicals. Absorption of vitamin C from food occurs in the small intestine, with a high yield, (70-80%), but at increasingly higher levels of consumption, (e.g. of 1 g/day), the absorption efficiency significantly decreases [7].

Adams and *Holloway* [2] studied the effect of moderate-dose multivitamin supplements, containing vitamin C, on autistic symptoms. Lower serum levels of vitamin C were observed in children receiving placebo than in children taking the supplement. It was found that high vitamin C doses may affect sleep disorders and gastrointestinal symptoms in people with ASD. This study however remains controversial as the other vitamins may also have had an impact on the results. Another study, by *Sankar* [76], however, demonstrated normal serum levels of vitamin C in ASD children.

Specialists consider that supplements are appropriate for autistic children with low serum Vitamin C levels as well as those with normal ones, as it has been shown that vitamin C supplementation may have positively

affect the pathological behaviour of people with ASD. It is thought that ascorbic acid prevents dysregulation of the brain signalling glutamatergic system, (which has been shown to be associated with ASD), thus reducing brain inflammation [9].

The action of ascorbic acid on ASD symptoms was studied in 18 ASD children, (divided into 2 experimental groups), by *Dolske* et al. [21] to see if it can be complementary to pharmacological treatment. The first group received ascorbate-ascorbate-placebo supplements lasting for 10 weeks, whilst the second ascorbate-placebo-ascorbate. The supplement was administered at a dose of 8 g/70 kg/day and results were evaluated by the *Ritvo-Freeman* scale. Ascorbic acid therapy showed a reduction in the severity of symptoms of autism. It should however be emphasised that vitamin C tolerances in people with ASD may be variable, therefore patients should be continuously monitored by a physician and dietician.

Vitamin A

Although nutritional status assessment is not one of the methods for diagnosing autism, it can significantly influence to the proper course of treating the symptoms. *Uyanik* et al. [81] reported an 8 year old child with ASD, that indicated vitamin A deficiency, resulting in xelophalmia and epileptic seizures. After interviewing the child, specialists found that the child had only consumed fried potatoes and drank water. Serum vitamin A was significantly reduced with a concentration of 10μg/l compared to a normal reference value of 50 μg/l. Subsequently, multivitamin therapy, (containing 5000 USP/mg vitamin A), resulted in behavioural improvements. The study found that less severe symptoms of vitamin A deficiency may also occur more frequently in patients with ASD.

Furthermore, a case study by *Megson* [62] indicated that vitamin A supplementation may be effective in treating symptoms of autism where it was concluded that there was an absence of a specific gene in ASD patients, encoding a protein essential in vitamin A synthesis. Here the therapy was seen improve language skills and in maintaining eye contact in two children with ASD. Further and comprehensive clinical studies are however required to confirm these findings.

It is important to note that any vitamin A supplementation should be conducted under the supervision of medical staff and a nutritionist, as there is only a small difference between therapeutic and toxic doses of retinol.

Vitamin D

In a report by *Grant* and *Soles* [34], vitamin D deficiency was examined in pregnant mothers to see if it may be a risk factor for childhood autism. It was thereby suggested that the an adequate intake of vitamin D or its supplementation may reduce the risk of autism by supporting the proper development of the brain and immune system.

Kalueff et al. [46] suggested that vitamin D has a neuro-protective effect and may affect the interaction of neurotransmitters in the brain, hormones and neurotransmitters, which can influence patient behaviour. In another report of *Kalueff* and *Tuohimaa* [47], the nootropics and pleiotropics properties of vitamin D were reviewed, where the merits of vitamin D supplementation were highlighted in cases of brain dysfunction associated with deficiency of vitamin D during clinical nutrition.

A mouse study [27] showed that vitamin D deficiency is a reliable biological risk factor for neuropsychiatric disorders and can act as a neuroactive steroid directly affecting brain development.

Vitamin B_{12} and folic acid

Vitamin B_{12} deficiency causes megaloblastic anaemia and disorders of the nervous system. It interacts with folic acid, whose deficiency is characteristic of people with intestinal dysfunction and epilepsy.

Pineles et al. [65] diagnosed reversible optic neuropathy arising from digestive vitamin B_{12} deficiency in 3 patients with autism, following an examination showing atrophy of the optic nerve and from interviewing the subjects which revealed serious eating disorders; particularly in the consumption of animal products. The treatment was by vitamin B_{12} replenishment, given intramuscularly, resulting an improvement of symptoms in all three patients. It was suggested that these cases represent evidence for nutritional deficiencies in children with ASD being the cause of the numerous medical problems.

Patients with ASD are known to have deficiencies of folic acid in the cerebrospinal fluid (CSF). This deficit may be explained by the action of circulating serum autoantibodies in ASD patients against folate receptors (FR). Autoantibodies to folate bind folate acid receptors and block folic acid synthesis, which inhibits the folate transport to the CSF in autistic patients with cerebral folate deficiency syndrome (CFD) [69]. This mechanism may be a common factor that plays a key role in the pathogenesis of ASD.

The aim of a study by *Ramaekers* et al. [68] was to determine whether ASD children presenting with neurological disorders are associated with CFD. Disruption of folate transport into the central nervous system was observed in 2 ASD patients which could be due to antibody binding sites blocking FR. Serum folic acid concentrations were comparable to the those in the control group, nonetheless despite normal folic acid levels in serum, folate concentrations in the CSF were low in 23/25 patients. Following oral administration of folic

acid supplements an improvement in these patients' health was observed after 12 months.

Hence the early detection of FR autoantibodies could be a key factor in preventing ASD and in choosing suitable therapeutic interventions for those still suffering from ASD. In addition, an appropriate diet containing foodstuffs rich in folate may be an alternative or support for pharmacotherapy and dietary supplementation.

Iron

Iron deficiency in patients with ASD can cause sleep and nervous system disorders. A study by *Dosman* et al. [22] investigated the relationship between low levels of serum ferritin, and sleep disorders in ASD children, (n=33). Here, an insufficient dietary iron intake was observed in 69% of pre-school and 35% of school-age children. Parents and carers complained about the ASD children presenting with gastrointestinal symptoms, suggesting that malabsorption syndrome could be the cause of iron deficiency. All the children then received oral iron supplements for 8 weeks however, prior to this treatment, 77% suffered from sleep disorders. During this treatment significant improvements were noted which may indicate a relation between iron deficiency and sleep disorders in the ASD children. After the iron supplementation, serum ferritin significantly increased from 16 mg/l to 29 mg/l, whereas there was no clear relationship between dietary iron and serum ferritin. The need for screening ASD children for iron deficiency was thus indicated.

Studies by *Latif* et al. [54] analysed serum ferritin levels in ASD children with *Asperger's* syndrome. Anaemia with iron deficiency was found in six of these children whilst 12 had low serum ferritin. Impaired cognitive function, slowing growth, impaired concentration and mood changes in autistic children may be associated with iron deficiency or anaemia. This study indicated that many of the ASD children had low serum ferritin which may be a factor in the development of ASD disorders in this population grouping.

Zink and copper

Autistic persons have lowered zinc in red blood cells by 40% thus constituting a risk of oxidative stress. Conversely an excess of zinc can adversely affect digestive system function. Despite this, zinc supplementation is being increasingly used as a permanent element of autism treatment [43, 61].

Zinc supplementation however reduces the concentration of copper in the body, which very frequently occurs in patients with ASD [61]. Copper may exhibit pro-oxidative properties and therefore supplementation of copper compounds is not necessary in patients with ASD; even small amounts of copper doses can cause behavioural symptoms to deteriorate. ASD patients have been observed to have a higher serum copper : zinc ratio of 1.63, compared to a group of normally developing individuals (1.15) [84].

Zinc supplementation can also cause a reduction of serum manganese concentrations. It is thereby recommended that manganese be administered with zinc in a ratio of 1:6, ie. 5 mg of zinc and 30 mg of manganese. Using manganese supplementation as a therapy can, however lead to an overdose and specialists should periodically monitor serum concentrations of iron [61].

Faber et al. [28] examined the prevalence of zinc deficiency, a low zinc / copper ratio and high and toxic concentrations of copper in the serum of ASD children. An average zinc : copper ratio of 0.608 was found which was well below the recommended cut-off value of 0.7 representing the lowest of the range for healthy children. This ratio can also be used as a marker of toxic heavy metals such as mercury in ASD children.

Walsh et al. [82, 83] gathered data on shortages and surpluses of zinc and copper from amongst more than 3,500 children with ASD, and concluded that doses of about 2-3 mg zinc/kg are necessary to achieve normal zinc levels in patients with ASD.

CONCLUSION

In conclusion we can state that autism may have important links to metabolic disorders of gastrointestinal system. A dietary therapy is insufficient alone to effectively treat autism. Many studies demonstrate the need to supplement the nutritional deficiencies of autistic patients with fatty acids omega-3, probiotics, vitamins and minerals in combination with medical and psychological interventions. A properly designed elimination diet tailored to the patient's individual may also lead to relief of the autism symptoms and the occurrence of gastrointestinal disorders. Parents and caregivers should therefore be aware of the benefits of nutritional therapy and need for proper monitoring the treatment of patients with ASD.

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Received: 17 August 2012
Accepted: 10 December 2012