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EC PSYCHOLOGY AND PSYCHIATRY
Review Article

A Critical Discussion of the Clinical Management of Dietary Supplementation in Children with Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder

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Received: December 10, 2020; **Published:** January 30, 2021

Abstract

Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) are both classified as neurodevelopmental disorders, affecting primarily young children and adolescents, stemming from biological/genetic and environmental origins that negatively influence neurobiological structures and leading to gastrointestinal discomforts. More precisely, toxins produced by pathogenic microorganisms' overgrowth, unnecessary employment of antibiotics, abnormalities in the activity of carbohydrate digestive enzymes and gut's mucosal lining disruptions result in alterations in children's neurological functioning. Central nervous system alterations adversely affect brain maturation, social interactions, and cognitive abilities. In this respect, dietary supplementations such as omega-3 and omega-6 long-chain polyunsaturated fatty acids and/or vitamins can be effectuated, potentially increasing the effectiveness of pharmacological medications. However, research findings divulge an unspecified consensus concerning optimal supplementation duration, exact dosages, consistent utilization of outcome measures, adherence to supplements, and their long-term behavioral and health effects. In addition, dietary supplements do not always enable for corrections of children's micronutrient deficiencies, contributing to excessive intake. Thus, it can be speculated that they cannot be provided solitarily since they depict developmental insensitivities in addressing all nutritional needs of Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder individuals. Accordingly, each individual's developmental needs and entire dietary patterns should be carefully considered for the elimination of comorbid health conditions. In conjunction with the development and validation of universally accepted dietary plan, this shall allow for the construction of a holistic and multidisciplinary approach to dietary treatment schemes that can fully benefit these populations and are especially adapted to their needs. Future research should further explore gluten/casein-free and other restrictive diets, along with the clarification of effective randomized controlled trials.

Keywords: *Attention-Deficit/Hyperactivity Disorder; Autism Spectrum Disorder; Central Nervous System; Developmental Needs; Dietary Supplements; Neurological Functioning*

Abbreviations

ASD: Autism Spectrum Disorder; ADHD: Attention-Deficit/Hyperactivity Disorder; PUFAs: Polyunsaturated Fatty Acids

Autism spectrum disorder and attention-deficit/hyperactivity disorder in young people

During the past decade, treatment of Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) has been brought under the microscope by scientific research. Both conditions are classified under neurodevelopmental disorders, with high prevalence rates, affecting mostly children and adolescents [1,2]. ASD entails chronic core and peripheral symptoms which are frequently portrayed in children such as social interaction difficulties, communication and language impairments, motor incoordination and sensory scarcities, stereotyped/self-stimulatory behaviors, self-destructive behavioral patterns, gastrointestinal symptoms, increased seizures, and hyperactivity [3-5]. Children with ASD are further susceptible to vitamin and mineral inadequacies due to their frequently displayed risky eating behaviors [6]. On the other hand, ADHD encompasses high levels of inattention which are age-inappropriate, impulsivity, and hyperactivity, leading to long-term repercussions in academic, social, and emotional contexts, as well as low quality of life [7]. Markedly, ASD and ADHD stem from genetic and environmental origins influencing individuals' neurobiological structures [8-10].

A neurobiological explanation of the prevailing theories behind the physiological symptoms: intestinal dysbiosis and opioid peptide excess theories

Gastrointestinal discomforts have been observed in children with ASD and ADHD (e.g. bloating, constipation, abdominal pain), leading to the construction of the Intestinal Dysbiosis Theory [11], suggesting that children's neuron synapses are altered by toxins produced by pathogenic microorganisms' overgrowth in the endogenous gut or unnecessary employment of antibiotics [12]. Additionally, it is suspected that abnormalities in the activity of carbohydrate digestive enzymes and gut's mucosal lining disruptions resemble neuropeptides that generate unforeseen inflammations coupled with proteins' (e.g. casein, gluten, gliadin) malabsorption, resulting in alterations in neurological functioning [13,14]. Such alterations adversely affect brain maturation, social interactions, attention, and learning [15]. In this respect, the Opioid Peptide Excess Theory [16] proposes that binding of neuropeptides to opioid receptors and their modulation of the brain's opioid levels cause significant impairments in the central nervous system, with ASD children's peptides not typically transforming into amino acids. For ADHD individuals, alterations in the microbiome-gut-brain axis may provide an etiological explanation of several ADHD symptoms [17,18]. The aforementioned neurolobiological explanations have further contributed to developments of dietary proteins administration plans (e.g. beta-casomorphin) to improve children's intestinal permeability, delivering dietary peptides to their bloodstream [19] for an immune response to be triggered, consequently affecting the central nervous system which is responsible for ASD and ADHD symptoms.

Alternative dietary intervention strategies

An array of psychoeducational and psychotropic interventions has emerged for the clinical management of induced behavioral discrepancies among children with ASD and ADHD [20]. However, their heightened popularity within the literature is not a presupposition of their absolute effectiveness/suitability to treat these conditions. Thus, alternative treatment modalities such as dietary supplementation are provided, oftentimes excluding medical supervision [21]. The contentious utilization of dietary interventions is voiced by researchers, maintaining that they should be effectuated following a gluten and/or allergy/intolerance diagnosis [22] while attaching particular caution over the interventions' unknown effects. Yet, insightful research and application of dietary interventions seems inadequate, containing several inconclusive findings.

Dietary supplementation management for children with autism spectrum disorder

Dietary supplementation of docosahexaenoic acids, omega-3 long-chain polyunsaturated fatty acids (PUFAs), and eicosapentaenoic acids has been generally considered a safe substitute treatment alternative, even potentially increasing pharmacological medications' effectiveness [23,24]. However, its safety does not necessarily antedate its efficacy of improving ASD core symptoms [21]. Only a few randomized controlled trials utilizing omega-3 long-chain PUFAs while comparing them to placebos have been conducted, with some of

them harboring significant communicative, behavioral, or linguistic enhancements, or disclosing positive amendments in the placebo conditions regarding behavior externalization [25,26]. In the same vein, no evidence *vis-à-vis* positive effects on social interaction or stereotypical behavior has been brought up. Supplementarily, González-Domenech., *et al*. (2019) [27] detected non-significant improvements in the behavioral component of children with ASD or changes in concentrations of urinary beta-casomorphin. Conversely, ameliorations in sensory difficulties and language development, reoccurring in ASD populations, have been observed following omega-3 and -6 long-chain PUFAs supplementation by some trials [28,29], but have been contradicted by Mankad and colleagues' (2015) [25] findings. In this regard, Stewart., *et al*. (2015) [6] conducted a cross-sectional study with the main objective of investigating micronutrient intake and dietary supplementation in children with ASD. The findings revealed that multivitamins and minerals were also insufficient to alleviate children's micronutrient deficits (e.g. vitamin D deficiency). Moreover, prominent issues of excess vitamin intake lead to the former conclusion that it is beyond ASD children's needs to receive such micro-nutritional substitute treatment options since they are not cautiously applied to them.

Thus far, research findings divulge an unspecified consensus with regards to optimal supplementation duration, exact fatty acids dosages, or consistent utilization of outcome measures. Notably, attrition rates from such studies can range from 0% to 58%, which renders them alarming as the dropouts' underlying reasons remain undetermined. It is suspected though that natural variability [30] or ASD symptoms intensification following fatty acids supplementation contributed to attrition issues. In addition, adherence to dietary supplements remains uninvestigated, which would be of prominent value for improving the interventions along with constant plateau effects during treatment termination [23,31].

Remarkably, vitamin/mineral/fatty-acid supplementations do not always enable for corrections of ASD children's micronutrient deficiencies, resulting in excessive intake, which is concerning given that, in contrast to the general pediatric population, children with ASD are more frequently administered with supplements [6]. Advances in the adequate consumption of vitamins E and D, potassium, choline, and calcium amounts are evident, concurrently though there are still insufficient intakes of micronutrients and vitamins in ASD children [32] and little is known about their long-term behavioral and health effects. This makes it plausible that subsequent dietary supplementation is more effective for older children rather than younger ones, since some identified side effects induced by their excessive use in the former population may lead to unfavorable outcomes [6,33]. Likewise, the possibility of ASD children not requiring different nutritional needs compared to the general pediatric population is conceivably disregarded by clinicians.

Dietary supplementation management for children with attention-deficit/hyperactivity disorder

Commonly employed pharmacotherapeutic schemes for ADHD have risen questions regarding medication's adverse impacts, and such complications have unveiled the need of searching for substitute treatment alternatives [34]. Apart from ASD, dietary compounds including micronutrients (e.g. vitamins, minerals, PUFAs) have been proposed to facilitate ADHD treatment, with several publications demonstrating reduction of persuading symptoms in children with iron, zinc, and magnesium deficiencies. Yet, supportive empirical evidence is inadequate and many questions still revolve around the scope of whether vitamin supplementation in necessary and efficacious.

Research investigations demonstrate that ADHD children's dietary patterns are different compared to dietary configurations of healthy individuals. Similarly to dietary approaches to ASD, micronutrients (vitamins and minerals), and PUFAs may induce facilitative ADHD treatment effects. ADHD individual's zinc, iron, or magnesium deficiencies are mitigated through utilization of respective minerals, possibly resulting in better quality of life [35]. Hemamy, Heidari-Beni, Askari, Karahmadi, and Maracy (2020) [36] probed supplementation of vitamin D and magnesium in children with ADHD. Their findings provided supportive evidence on effective dietary supplementations, since children's serum levels significantly increased, and reductions in conduct difficulties, anxiety, and social impairments were ascertained. However, psychosomatic impediments were not substantially affected. In a similar manner, Richardson and Montgomery (2005) [37] conducted a trial to compare omega-3 and omega-6 dietary supplementation effects in children suffering from developmental co-

ordination disorder with comorbid ADHD symptoms. Incoordination was not improved but a sequence of ADHD symptomatology was alleviated, suggesting a potential genetic correlation with metabolism of fatty acids. Yet, more recent findings suggest otherwise; small effect sizes and no effects overall of PUFA supplementation have been displayed [38,39].

Research designs' heterogeneity, probable insufficient supplement dosages and duration, and variety in assessment methods may likely influence the overall effectiveness of dietary supplementation for ADHD individuals [40]. In relation to PUFAs, merely employing omega-6, omega-3, or a combination of the two, administrating them via means of supplements or fish, and ratio differentiations between PUFAs' blood levels may pose certain obstacles on their adequacy as a treatment approach [41,42]. Notwithstanding the foregoing, it is expected that application of supplements is a controversial and intermittent topic within ADHD literature; absence of ADHD biomarkers hinders micronutrients' effectiveness, identification, and validity. Underlying environmental and biological mechanisms of ADHD are multidimensional [43] and the assumption of dietary supplements' inclining more towards a one-fits-all approach doubtfully constitutes them a supremely effective intervention plan because they partially fail to acknowledge the condition's complex essence.

Undesirable side-effects of prolonged PUFAs' and vitamins' administration may consequently inevitably occur. These include susceptibility to prostate carcinoma, diabetes, adverse reactions, and DNA mutations (as was found in animal studies employing oxidized lipids) [44]. Also, high concentrations of PUFAs during pregnancy may culminate in the emergence of the offspring's subclinical ADHD symptoms throughout childhood and subsequent life span [45]. As such, the issue of considering each individual's developmental level and carefully provisioning supplements according to their developmental needs is of paramount significance [40]. Otherwise, importance should be stationed towards an ADHD individual's entire diet, instead of solely concentrating on specific micronutrients, which does not certainly eliminate low adherence effects, but definitely constructs a more holistic approach to dietary treatment [46]. Nevertheless, most ADHD individuals adhering to westernized patterns of diet are prone to experiencing persisting symptoms [47], elucidating an urgent requirement of developing and validating universally accepted dietary plans.

Conclusion

Although dietary supplements are highly popular, they cannot account for comorbid gastrointestinal conditions such as celiac disease (otherwise specified as gluten-sensitive enteropathy) which, by triggering an automatic immune response when children consume grain-based products, injures the small intestine [31]. As it can be postulated that certain dietary proteins may actually indirectly provoke impaired digestions, following more specialized diets (e.g. gluten/casein-free), these are expected to be normalized/stabilized [48], highlighting the need of further considering gluten/casein-free and other restrictive diets as well [49-50] towards reducing ASD and ADHD symptomatology, while cautiously detecting adverse side effects. This, in turn, unveils a complementary major issue of dietary supplements; the speculation that they cannot be provided solitarily can be postulated, since they seem to depict developmental insensitivities with regards to addressing all nutritional needs of children. It is proposed that their integration into a uniform or multidisciplinary treatment plan could benefit these populations. This leads to the ultimate conclusion that dietary supplementation requires more research, and exponential delicacy should be placed towards the clarification of effective randomized controlled trial designs and the application of supplementations that are especially adapted to each individual's developmental prerequisites.

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