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RESEARCH ARTICLE

A COMBINED MEGAVITAMIN AND COMPLEX HOMEOPATHY REGIMEN IN CHILDREN WITH AUTISM SPECTRUM DISORDER PROMOTES SPEECH DEVELOPMENT: A CASE SERIES

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ABSTRACT

Introduction: There are currently no approved pharmacological therapies for the core symptoms of autism spectrum disorder (ASD), prompting nearly half of patients or their carers to seek complementary and alternative medicine approaches. There is now compelling clinical and basic scientific evidence that megavitamin therapy can help relieve the core symptoms of ASD, perhaps by modulating cellular energy metabolism and oxidative stress. While many patients also use homeopathic preparations, there are very little data on their efficacy. **Case presentation:** Based on these data and underlying rationale, a new integrative medicine approach was designed for ASD that combined parenteral B and C megavitamin therapy and a complex homeopathic preparation designed to target the core features of ASD pathobiology. The approach was tested in three young children with ASD, all of whom exhibited a significant increase in their spoken vocabulary and a noticeable improvement in interaction skills after three months of therapy. **Discussion:** This is only the third report of the use of a homeopathic preparation is ASD and the first report of its rational combination with megavitamins. The impressive symptom resolution and absence of side-effects seen here suggest that this integrative medicine approach is a promising intervention for children with ASD and should be further studied in larger clinical cohorts.

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INTRODUCTION

Autism spectrum disorder (ASD) describes a heterogenous group of complex neurodevelopmental disorders with common core social interaction symptoms including communication impairment, restricted interests, and repetitive behaviors (Lai, 2014). The worldwide prevalence of ASD is estimated to be between 1 and 2%, the disorder affects 4-5-times more males than females, and the prevalence is increasing, mainly due to enhanced recognition and awareness, improved diagnosis, and younger age at diagnosis (Lai, 2014). Individuals with ASD have an approximately three-times greater mortality risk than unaffected age- and sex-matched individuals, mainly due to co-morbid conditions, and many adults with ASD suffer from life-long impaired quality of life and underachievement of occupational potential (Howlin, 2013). There is therefore an urgent need to improve outcomes for individuals with ASD, particularly with respect to the core symptoms. Interventions for ASD can be broadly classified into behavioral and pharmacological.

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Behavioral approaches, which target a wide range of skills through long-term intensive programs of applied behavioral analysis and structured teaching, have shown efficacy at a moderate level of evidence, particularly when initiated early in development (Tachibana, 2017). From the pharmacological perspective, while antipsychotic drugs have been shown to reduce challenging and repetitive behaviors, particularly in younger children, evidence for efficacy in adults is lackingand adverse effects can be problematic (McPheeters, 2011). However, no drug therapy has a proven benefit in relieving social communication deficits, prompting many patients and parents to seek alternative therapies to improve quality of life; approximately 45% of adults with ASD have used complementary and alternative medicines (CAMs) at some point in their lives (Hofer, 2019). Of the various alternative approaches available, nutritional supplementation with vitamins, minerals, amino acids, omega-3, and herbal compounds are popular. Indeed, a very recent meta-analysis of 27 randomized double-blind controlled trials showed that dietary, omega-3, and vitamin supplementation were all more effective than placebo at improving ASD symptoms and patient function(6). Vitamin supplementation was more effective than placebo in treating global severity, language, stereotypies, restricted andrepetitive behaviors, behavioral problems and impulsivity, hyperactivity and irritability, and

various clinical domains including core symptoms, albeit with small effect sizes (Fraguas, 2019). Although over a quarter of adults with ASD have used alternative medicines such as homeopathy and naturopathic medicine, evidence on their efficacy is scarce (Hofer, 2019), with only two published studies on homeopathy use in ASD currently available; the first in 12 adults reporting that homeopathic secretin given weekly for 12 weeks demonstrated some worsening of behavior during treatment (Robinson, 2001), and the second a case series of six children who experienced improvements in core symptoms and communication deficits after being administered an appropriate similimum for each particular case (Rajalakshmi, 2009). This case series describes three young children with ASD treated with a combination of parenteral B and C megavitamin therapy and a complex homeopathic preparation designed to target core features of ASD pathobiology, namely antioxidant defects and defective cellular metabolism. All three children exhibited a significant increase in their spoken vocabulary and a noticeable improvement in interaction skills after three months of therapy.

Case Presentation and Presenting Concerns: Three children aged 3.2, 3.5, and 3 years of age (weights 15, 17, and 16 kg)presented to clinic with ASD as defined by DSM-5 criteria including difficulties in social communication and social interaction and restricted and repetitive behaviors. In particular, the children exhibited difficulties in expressive phonology and grammar, only speaking two-three meaningful words per week (child 1: mummy and yummy; child 2; bye bye and gimme; and child 3 mummy, daddy, and no). All children had been attending intensive speech therapy for several months to no effect. The patients' parents gave informed consent for treatment.

Therapeutic Intervention and Treatment: The children were prescribed a three-month course of combined megavitamins and Coenzyme Compositum (Heel, Germany; patent reference: PCT HR 2010/000015) as subcutaneous injections, since oral compliance with oral medications is poor in children and subcutaneous administration maximizes bioavailability. The megavitamin preparation contained vitamins B6 (5 mg), B1 (20 mg), vitamin B12 (100 μg), and vitamin C (20 mg), while Coenzyme Compositum was as described previously (Novak, 2013; Novak, 2019). Briefly, Coenzyme Compositum is available in 2.2ml vials as an over-the-counter preparation andcontains compounds involved in the Krebs cycle, as well as herbal homeopathic remedies, all present in equal volume (Novak, 2013; Novak, 2019). The patients received their injections each working day in clinic under medical supervision to ensure correct subcutaneous administration and consistency. Gluteal skin was anesthetized with 0.5% Emla (lidocaine/prilocaine) cream prior to subcutaneous injection using a 5 ml syringe and insulin needles, once daily at 10 am. Two subcutaneous injections were given, the first containing the B vitamins diluted in one 2.2 ml vial of Coenzyme Compositum, and the second containing vitamin C diluted in another 2.2 ml vial of Coenzyme Compositum.

Follow-up and Outcomes: After three months of therapy, all three children had increased the number of meaningful spoken words per week: child 1, 18 words (mummy, daddy, bye, own name, no, yes, petname, kitty, puppy, teddy bear, chicken, juice, milk, tractor, nose, tree, birdy); child 2, 19 words (mummy, daddy, grandma, auntie, bye, chicken, bunny, puppy, wannaeat, teddy bear, doll, thank you, let's go home, banana); and child 3, 15 words (mummy, daddy, grandma, auntie, bye, yummy, kitty, puppy, no, eat, go, bread, cake, ice cream). This increase in the number of spoken words was significantly different (average 2.3 words before therapy to an average of 17.3 words after therapy; Student's t-test p=0.01).Furthermore, eye-to-eye contact had increased and there was a noticeable improvement in interactions with toys.On the clinical global impression improvement scale, the score was 2 (much improved) (Busner, 2007). Aside from discomfort at the site of application, no other side effects were observed. The urine was noted to have changed in odor and color, consistent with high vitamin B intake.

DISCUSSION

Currently available drugs for the treatment of ASD mainly target co-occurring symptoms such as aggressive or self-injurious behaviors, irritability, and outbursts, with two atypical antipsychotics (aripiprazole and risperidone) currently licensed by the US Food and Drug Administration (FDA) for this purpose (Goel, 2018). However, no drugs are available for the treatment of the core symptoms of ASD, namely impairments in communication and social interaction and the presence of restricted and repetitive behaviors. This prompted the present study, which examined the use of a B and C megavitamin preparation combined with a complex homeopathic preparation administered parenterally. By using this integrative medicine approach, paradigmatically different therapeutic actions were combined with the hope of magnifying the therapeutic potential. The use of CAMs, especially nutritional supplements in the form of vitamins, is a promising strategy to reduce symptom burden in ASD patients while avoiding harmful side-effects. The causal relationship between the pathogenesis of ASD and multivitamin intake is supported by several lines of evidence. First, population-based studies have shown that multivitamin intake during gestation may be associated with a decreased risk of ASD in newborns, with mothers of ASD children less likely to have taken vitamin supplementation before and after conception (Schmidt *et al*., 2011) or during pregnancy (DeVilbiss, 2017). Second, an interventional study showed that multivitamin supplementation administered to ASD children for three months can improve sleep, reduce ASD symptoms, and improve biomarkers of energy production and oxidative stress (Adams *et al*., 2011).

Third, megavitamin (i.e., doses above recommended dietary allowances (RDA)) administration of vitamin B6 and magnesium has been shown to improve social interactions, communication, and stereotyped restricted behavior in ASD children (Mousain-Bosc, 2006). Fourth, three months of dietary supplementation with vitamin B12 in combination with glutathione (GSH) and a low fructose/organic diet improved concentration, social interactions, behavior, and speech in ASD children (Patel, 2007). Fifth, A 30-week, double-blind, placebo-controlled study of high-dose vitamin C (110 mg/kg) reported a reduction in autism severity (Dolske, 1993). Finally, lower vitamin B levels have been detected in ASD children compared to age-matched controls (Ali, 2011). Therefore, there is compelling clinical evidence that vitamin deficiency is associated with ASD pathobiology and that vitamin replacement might therefore be an effective treatment for the condition. Although the etiology of ASD remains uncertain, oxidative stress and defective energy metabolism are both implicated in its pathogenesis. Reducing plasma GSH increases the oxidized: reduced GSH ratio, and antioxidant

enzymes such as glutathione peroxidase, catalase, and superoxide dismutase are often impaired in individuals with ASD (Ghanizadeh, 2012). Furthermore, mitochondrial dysfunction and abnormal adenosine triphosphate (ATP) levels have been detected in the blood and brains of ASD patients (Al-Mosalem, 2009; Siddiqui, 2016; Theoharides, 2013). Taken together, the underlying etiology of ASD and the clinical data prompted the current therapeutic approach. B vitamins are critical mediators of catabolic energy metabolism, including in the brain (Kennedy, 2016), and also possess anti-oxidant functions via multiple mechanisms including directly and indirectly scavenging reactive oxygen species (ROS) and modulating cytokine and growth factor production to protect immune response-induced oxidative stress (van de Lagemaat, 2019). Vitamin C is a critical central nervous system antioxidant,deficiency of which is implicated in both neurodevelopmental defects and cognitive decline (Hansen *et al*., 2014). The homeopathized (potentized) Krebs cycle components used in the study act as non-specific metabolism activators ((Witt *et al*., 2007), according to the Reckeweg theory of isopathy and homotoxicology). Therefore, although the exact mechanism of action remains to be determined, the current approach was selected to positively impact neurological oxidative stress and energy metabolism, hypothesizing that the homeopathic preparation used here may induce small changes in cellular energy production that synergize with the administered vitamins to improve their efficacy.

The doses of vitamins B6 (5 mg; RDA 1.3-1.7 mg), B1 (20 mg; RDA 1.1-1.2 mg), vitamin B12 (100 µg; RDA 2.4 µg) and vitamin C (20 mg; 75-90 mg) administered in this study were supraphysiological. However, the use of megavitamin preparations in neurological disease dates to the 1950s for the treatment of schizophrenia, and vitamin B6 was used as early as the 1960s in autistic children with observable improvements in speech and language (28). Although a Cochrane review of three high-quality clinical trials studying the use of megavitamin vitamin B6 in ASD was unable to recommend high-dose vitamin B6 for ASD, with the trials as reported not detecting significant differences in behavioral outcomes, only thirty-three patients were available for analysis in total, the small sample sizes severely limiting the analyses, as noted by the authors (Nye, 2005). However, a very recent meta-analysis reported that vitamin supplementation was more effective than placebo in treating global severity, language, stereotypies, restricted and repetitive behaviors, behavioral problems and impulsivity, hyperactivity and irritability, and various clinical domains including core symptoms, albeit with small effect sizes (Fraguas, 2019). Furthermore, although there was methodological heterogeneity between the analyzed studies in terms of the intervention, clinical measures and outcomes, and sample characteristics, the studies included in the meta-analysis had low statistical heterogeneity and low risk of publication bias. Therefore, further research into megavitamin and homeopathy use in ASD using larger, randomized trials is needed, with the currently proposed regimen a possible option for further rigorous testing. Even in the early reports of megavitamin therapy in ASD (Rimland, 1978), concern was raised about the possibility of adverse effects, and long-term vitamin B6 use could be associated with mild neuropathy (Schaumburg, 1983; Omaye, 1984). However, there were no adverse effects either in the reported trials (Nye, 2005) or the current series, most likely due to the relatively short-term and limited administration of the preparations.

Nevertheless, further work is needed to clarify the optimal duration of therapy and possibility of adverse effects in the context of an appropriately monitored clinical trial. While conventional medicine is mainly based on a biochemical paradigm, for instance the action of drugs acting on cellular receptors, the actions of homeopathic medicines are poorly understood, since the quantity of diluted matter is so small that it cannot satisfy the receptor theory in the biochemical paradigm (Bell, 2004; Taylor, 2000). There are disputes about the efficacy of homeopathic medicine, which remains controversial. Although it is widely suggested that homeopathy works via a placebo effect, there are competing opinions (Linde, 1997; Ludtke, 2008; Vickers, 2006) and a growing set of theories as to the mechanism of action, which have changed over the past 150 years and continue to do so. While the homeopathic preparation may have induced small changes in cellular energy production that synergized with the vitamins, several limitations need to be highlighted. First, this was a small, non-randomized observational case series, so bias may have enhanced any placebo effect of homeopathy or the vitamin preparation. Second, the children also continued to receive speech therapy during the study, which may have given rise to the observed effects; however, the speech therapy is unlikely to have impacted the social interaction skills, which also improved. Nevertheless, this is only the third report of the use of a homeopathic preparation is ASD and the first report of its rational combination with megavitamins. The impressive symptom resolution and absence of side-effects seen here suggest that this integrative medicine approach is a promising intervention for children with ASD and should be further studied in larger clinical cohorts.

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