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Can we predict treatment response in children with ADHD to a vitamin-mineral supplement? An investigation into pre-treatment nutrient serum levels, *MTHFR* status, clinical correlates and demographic variables

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ABSTRACT

Background: Intent-to-treat analyses from a randomized controlled trial showed significant between-group differences favouring micronutrient treatment on the Clinical Global Impression-Improvement, but no group differences on clinician, parent and teacher ratings of overall ADHD symptoms. There was an advantage of micronutrients over placebo in improving overall function, emotional regulation, aggression, and reducing impairment as well as improving inattention based on clinician but not parent observation. No group differences were observed on hyperactive-impulsive symptoms. We investigated predictors of response defined by pre-treatment variables.

Method: We conducted analyses of data from a clinical trial of children (7–12 years) with ADHD, whereby participants were randomized to receive micronutrients or placebo for 10 weeks followed by a 10 week open-label (OL) phase. We included only children who had been exposed to micronutrients for a full 10 week period and demonstrated satisfactory adherence, either in RCT phase (n = 40) or OL phase (those who received placebo during RCT phase; n = 31). Seven outcomes were examined: change in ADHD symptoms (clinician/parent), ADHD responder, overall responder, change in mood, change in functioning, and change in aggression. Demographic, developmental variables, current clinical and physical characteristics, *MTHFR* genotype at two common variants, and pre-treatment serum/plasma levels (vitamin D, B_{12}, folate, zinc, copper, iron, ferritin, potassium, calcium, magnesium, and homocysteine) were all considered as putative predictors.

Results: Substantial nutrient deficiencies pre-treatment were observed only for vitamin D (13%) and copper (15%), otherwise most children entered the trial with nutrient levels falling within expected ranges. Regression analyses showed varying predictors across outcomes with no one predictor being consistently identified across different variables. Lower pre-treatment folate and B_{12} levels, being female, greater severity of symptoms and co-occurring disorders pre-treatment, more pregnancy complications and fewer birth problems were identified as possible predictors of greater improvement for some but not all outcome measures although predictive values were weak. Lower IQ and higher BMI predicted greater improvement in aggression.

Conclusions: This study replicates Rucklidge et al. (2014b) showing the limited value of using serum nutrient levels to predict treatment response although we cannot rule out that other non-assayed nutrient levels may be more valuable. Additionally, no specific demographic or clinical characteristics, including *MTHFR* genetic status, were identified that would preclude children with ADHD from trying this treatment approach.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder affecting approximately 5% of children (American Psychiatric Association, 2013) that is associated with ongoing psychiatric problems in adulthood, unemployment, school failure and incarceration (Klein et al., 2012; Molina et al., 2009; Hechtman et al., 2016). The most evidence-based treatments for ADHD are

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pharmacological; however, because of potential side effects and failure to prevent or alter long-term course, they can be perceived as an unattractive choice for some families (Swanson et al., 2017). As such, attention has widened to investigate other treatment options.

Consideration of the role that nutrition plays in the expression of ADHD has re-emerged over the last few years with food dyes, processed foods, and low consumption of fruit and vegetables all shown to have an association with ADHD symptom severity (Howard et al., 2011; Pelsser et al., 2011; Rios-Hernandez et al., 2017). However, other variables are also potentially relevant to brain health. For example, poor gut health, microbiome composition (Dinan & Cryan, 2017; Dinan et al., 2018; McNally et al., 2008), inflammation (Oddy et al., 2018), genetic variants that influence metabolism (Ames et al., 2002), and mitochondrial dysfunction (McNally et al., 2008; Toker & Agam, 2015; Kaplan et al., 2015), have all been identified as possible factors that may influence psychiatric disorders and contribute to the need for more nutrients than might be available in consumed food. The presence of any or all of these factors could effectively reduce the availability of nutrients for optimal brain health. Considering all these factors, supplementation may need to be considered over and above the manipulation of diet.

To date, the treatment of ADHD with a single nutrient approach has resulted in small and inconsistent findings (Hariri & Azadbakht, 2015). Based on research conducted in our lab, we have speculated whether multi-ingredient treatment approaches may result in more consistent treatment effects (Gordon et al., 2015; Rucklidge et al., 2011; Rucklidge et al., 2018; Rucklidge et al., 2014a). Given ADHD is a complex heterogeneous disorder, it has been suggested that intervening with one nutrient is highly unlikely to yield large effects (Mertz, 1994). A number of factors also lend support to the hypothesis that multinutrient approaches are worthy of investigation. From a physiological perspective, multiple nutrients are required in biological processes such as the methylation cycle and the Krebs cycle and it may be advantageous to combine nutrients to maximize metabolic function. Neurotransmitters, including dopamine and nor-adrenalin, which are implicated in ADHD (Thapar & Cooper, 2016), undergo several metabolic steps in relation to synthesis, uptake, and breakdown. Each of these steps is dependent upon multiple co-enzymes (cofactors), most of which include a variety of vitamins and minerals. Therefore, it appears reasonable to investigate a combination of a comprehensive range of micronutrients at doses expected to be sufficient to elicit a possible response without being likely to cause adverse effects in the majority of participants.

When investigating any new treatment, not only is it important to establish safety and efficacy, but also to establish who may benefit the most from the treatment. Understanding what treatments work for whom and what pre-treatment factors predict treatment outcome are common investigations in clinical trials, although predictors often tend to be weak and not replicated across studies. For example, ADHD subtype predicted change in behavioural regulation to a cognitive training intervention for those with combined subtype showing greater change relative to inattentive subtype (van der Donk et al., 2016). Based on the Multimodal Treatment Study of Children with ADHD (MTA) trial, comorbid anxiety appears to increase response to behavioural treatments but gender and comorbid disruptive disorders did not moderate treatment outcome (The MTA Cooperative Group, 1999). Antshel and Remer (2003) found that conduct and oppositional defiant disorder symptoms predicted poorer response to social skills training but other studies don't replicate this finding (Ollendick et al., 2008). Buitelaar et al. (1995) determined that younger age, high IQ, lower symptom severity, greater inattention, and low rates of anxiety predicted better response to methylphenidate. However, other studies have not found symptom severity to be a useful predictor. For example, Johnston et al. (2015) found that reduced impulse control and comorbid conduct disorder predicted response to methylphenidate but symptom severity proved less useful in prediction. Overall, no one variable stands out as a consistent predictor to both pharmacological and nonpharmacological treatments in ADHD research.

Biochemical markers (biomarkers) have been increasingly studied in attempts to identify those who might be at risk for ADHD as well as who might benefit from a treatment (Scassellati et al., 2012). Some biomarkers are modifiable and may lead to targeted treatments. With nutritional interventions, it is therefore important to determine whether pre-treatment nutrient levels might assist with determining response to a broad-spectrum combination of nutrients. Although many nutritional deficiencies have been associated with ADHD symptoms such as magnesium, zinc, iron, vitamin D, vitamin B_2, B_6 and B_9 (Kamal et al., 2014; Bener & Kamal, 2013; Bener et al., 2014; Greenblatt & Delane, 2017; Landaas et al., 2016), to date only one study has looked at nutrient biomarkers as predictors of treatment outcome (Rucklidge et al., 2014b). That study found that lower levels of vitamin D and copper were possible predictors of response but overall effects were small and inconsistent across different outcome measures.

This current study presents a replication of Rucklidge et al. (2014b), analyzing whether nutrient biomarkers taken prior to micronutrient treatment are useful for predicting treatment response in children with ADHD. These predictors were explored alongside more commonly investigated predictors including demographic variables, developmental history, *MTHFR* genotype at two common variants, and clinical correlates. This current investigation into predictors is based on a fully blinded RCT that showed benefit for one of three primary outcomes as well as a number of secondary outcomes. Specifically, there was an advantage of micronutrients over placebo in improving overall function, emotional regulation, aggression, and reducing impairment as well as improving inattention based on clinician but not parent observation. No benefit of nutrients over placebo was observed for hyperactive/impulsive symptoms (Rucklidge et al., 2018).

2. Methods

2.1. Study design

The study was approved by the university and national institutional review boards. After describing the experimental nature of the trial and explaining the other treatment options available in the community, written informed consent/assent was obtained. The trial was prospectively registered (ACTRN12613000896774).

Comprehensive study details have been described previously (Rucklidge et al., 2018). In brief, this was a 10 week double-blind (participants and investigators), parallel–group RCT designed to assess the efficacy and safety of a broad spectrum micronutrient formula (Daily Essential Nutrients (DEN)) compared with placebo, followed by a 10 week open-label (OL) trial with DEN in 93 medication-free children with ADHD, 7–12 years. Participants had to meet criteria for ADHD based on the Kiddie Schedule for Affective Disorders and Schizophrenia Lifetime Version (K-SADS-PL) (Kaufman et al., 1997), as well as parent and teacher Conners Rating Scales-Revised (CRS-R; T score $>$ 65 on parent form and $>$ 60 on teacher form) (Conners, 1997). The K-SADS was also used to identify co-occurring conditions.

The K-SADS has excellent instructions for ratings and previous research has shown robust reliability and validity data (Kaufman et al., 1997). The K-SADS interviews were conducted by doctorate-level clinical psychologists or clinical psychology graduate students and trained on appropriate administration of the interview via training videos as well as through observation by a clinical psychologist. All interviewers had established excellent interrater reliability through training. Interviews are regularly reviewed by a second rater to maintain and review reliability of the diagnoses. For cases not observed for reliability, every case is reviewed with the PI (a clinical psychologist) prior to a diagnosis being made. Participants were also seen by our study psychiatrist.

Participants took three capsules per day initially, divided into three doses to be taken with meals and water, increasing to six capsules per