A Pilot Study Evaluating the Effect of Vitamin D on Clinical Outcome in Autistic Children

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Abstract

Background:

Vitamin D deficiency has been proposed to have an important role in the development and progression of autism spectrum disorders (ASDs) with no prior randomized controlled trials. Objectives: To determine the efficacy and safety of high doses of vitamin D compared to placebo in treating autistic children.

Methods: This was a double- blinded placebo controlled trial. ASD patients were randomized to receive either 1000 international units of vitamin D per day for 3 month , followed by 1000 international units per 25 pounds per day (average dosing was 2800 IU/day) for another 3 months (n=22) or placebo (n=20) . The primary outcome measures were changes in Childhood autism rating scale (CARS) and Autism treatment evaluation checklist (ATEC) scores. Secondary outcome measures were the changes in serum vitamin D levels as well as treatment emergent side effects. Also, dietary vitamin D intake and sun exposure hours were collected using an adapted pre-validated food frequency questionnaire. Vitamin D intake was compared with recommended dietary intake (600 IU).

Results: Autistic children had significantly lower serum levels of 25- hydroxy vitamin D than healthy children ($P < 0.001$) with 54.7% and 28.6% being vitamin D deficient and insufficient, respectively. Dietary vitamin D intake of both groups was significantly lower than recommended dietary intake

After 6 months of therapy, there were statistically significantly greater improvements in CARS (4 points) and ATEC overall scores (16 points) in vitamin D group compared to placebo ($p<0.001$) and 31.8% of patients shifted from severe range to mild –moderate range and 63.3% of patients reached cut-off point of 30 .

No correlations were evident between serum vitamin D levels and either CARS or ATEC scores or between serum vitamin D level and either dietary vitamin D intake or Childhood Autism Rating Scale.

Conclusions: Vitamin D was tolerable and significantly improved clinical measurements of ASD severity.

List of Abbreviations

AAP: American academy of pediatrics

ABA : Applied behavioral analysis

ASD: Autism Spectrum Disorders

ATEC: Autism treatment evaluation checklist

ATP: Adenosine triphosphate

BH4: Tetrahydrobiopterin

CARS: Childhood Autism Rating Scale

DMSA: 2, 3 dimercaptosuccinic acid

GST: Glutathione transferase enzyme

LBW: low birth weight

MCP-1: Monocyte chemoattractant protein-1

MMR : Measles Mumps Rubella

MRI : Magnetic resonance imaging

MtD: Mitochondrial dysfunction

5-MTHF: 5- methyltetrahydrofolic acid

NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells

PDD: Pervasive Developmental Disorders

RXR: retinoid X receptor

TEACCH: Treatment and Education of Autistic and Communication Handicapped Children

TNF-α : Tumor necrosis factor alpha

TPH: Tryptophan hydroxylase

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Autism spectrum disorders (ASDs) are a heterogeneous group of complex, biologically based neurodevelopmental disorders. Their aetiology is still unknown and somewhat controversial. Although there is a large consensus regarding a key genetic role in the condition, an increasing body of evidence suggests that environmental factors may also be implied, in conjunction with the genetic factors and acting very early in development**(Cannell, 2010, Kinney et al., 2010, Coleman et al., 2011)** The gene-environment interaction hypothesis **(Freitag et al., 2010)** investigated for several other medical and psychiatric conditions **(Uher, 2014)**, has been recently suggested for ASD a putative role of vitamin D deficiency has been proposed **(Bakare et al., 2011, DeLuca et al., 2013, Neggers, 2014)**

Vitamin D has an important role in brain homeostasis as well as gene regulation **(Ramagopalan et al., 2010, Harms et al., 2011, Sigmundsdottir, 2011)** modulation of immune function **(Hayes et al., 2003)**, cell proliferation and apoptosis, and brain development and function as well as many neuroprotective properties **(Holick, 2007)** against cognitive impairment and neurological conditions in general **(Berquist et al., 2007, Anastasiou et al., 2014, Annweiler et al., 2014)**

Vitamin D, whose main sources in humans are sun exposure and food intake **(Norman, 1998, Anastasiou et al., 2014)**, is well- known to have

several positive effects. An apparent epidemic of vitamin D deficiency is now being recognised **(Holick, 2007, Adams et al., 2010)** as a major public health problem worldwide in all age groups despite abundant sunshine in many countries **(Dawodu et al., 2015).** Vitamin D deficiency has been proposed as an important key player in development of ASD **(Fernell et al., 2010, Meguid et al., 2010),(Molloy et al., 2010), (Duan et al., 2013).**

Children with ASDs often exhibit behaviours that result in feeding problems and, in turn, may impact nutrient intake. They tend to desire sameness in daily routines including eating the same foods that result in a diet that lacks variety **(Moore et al., 2012)** Additionally, disturbances in routine may lead to disruptive mealtimes, and, thus poor intake. Other possible factors that may affect nutritional status include gastrointestinal (GI) complications as well as differences in metabolism and utilization of nutrients. Difficulties in dietary intake of nutrients such as calcium and Vitamin D in children with ASD have been found **(Hyman et al., 2012, Williams-Hooker et al., 2013, Keown et al., 2014).**

Researchers have begun to explore the importance of vitamin D which forces the American Academy of Paediatrics in 2008 to recommend higher intakes based on evidence from clinical trials and the history of safe use of 400 IU/day of vitamin D in paediatric and adolescent

populations which increased in 2010 to reach 600 IU per day for children aged above 1 year **(Abrams.S.A, 2011)**

All these factors make it imperative to examine the adequacy of nutrient intake in children with autism. Few studies have compared food and nutrient intake of children with AD to children with typical development or to standard values. Moreover, It remains under debate whether children with autism should be supplemented with high doses of vitamin D in order to maintain optimal 25(OH) D concentrations or not **(Wang et al., 2015)** .Few open labeled studies have suggested the introduction of vitamin D as a treatment for autism spectrum disorders **(Cannell et al., 2013) (Cannell 2013, Jia et al., 2015, Saad et al., 2015)**. However, there was a need to carry out a double blinded placebo controlled trial with an adequate dose of vitamin D to challenge the theory that introducing vitamin D to autistic patients may improve autistic symptoms.

Autism spectrum disorder

1. Definition

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with "impairments in social interaction, communication with repetitive and restricted behavior". It usually starts before 2 years of age **(PsychiatricAssociation., 2013).**

2. Prevalence

Autism is a global health crisis that knows no borders. It does not discriminate individuals, based on nationality, ethnicity or social status. Centers for Disease Control and Prevention, conducts year-round studies that relate to and indicate the incidence and prevalence of autism to reach 1 in 45 child to develop ASD with an inexplicable male bias **(Zablotsky et al., 2015).**

3. Behavioral features of autism spectrum disorder

3.1 Reciprocal social interaction

Difficulties and delay in social interaction are often the earliest features in ASDs, but they can be subtle and easily missed. Absence of joint attention (i.e. failure to show interest, share a focus of attention and follow gaze) is highly suggestive of core autism **(American Psychiatric Association., 2000).**

3.2 Communication

The verbal and nonverbal communication deficits seen in ASD are varied and complex. The deficits range from complete failure to develop expressive and receptive language skills to fluent speech with specific

semantic or pragmatic impairments **(Tuchman, 2003).** Nonverbal communication deficits include a profound lack of gestural communication **(Network, 2007).**

3.3 Restricted interests and repetitive behaviors

Activities in individuals with ASD are often restrictive and repetitive with routines. The pattern of restricted interests in these individuals can be extremely varied (eg, cars, dinosaurs, trains, weather, numbers and letters, books, telephone directories, escalators and elevators)**(Fuentes et al., 2014).**

3.4 Sensory abnormalities

Although not part of the diagnostic criteria, abnormal sensory behaviors, such as significantly increased or decreased sensitivity to various sensory inputs, are often reported in children with ASDs **(Bryson et al., 2003)**.These sensory deficits are believed to be originated from that brainstem abnormalities, specifically in gray matter structure **(Jou et al., 2009).**

3.5 Regression

Autistic children who lose their language, social interaction, and other developmental milestones although they have normal development until the age of 1 to 2 years are described by the term "Regressive autism" **(Newmark, 2007).**

4. Etiology

The exact cause of autism is still unclear but genes and the environment are thought to play an important role **(Schieve et al., 2012)**. ASD has a strong genetic component, with heritability estimated to be as