Nutritional Neuroscience
An International Journal on Nutrition, Diet and Nervous System

ISSN: 1028-415X (Print) 1476-8305 (Online) Journal homepage: http://www.tandfonline.com/loi/ynns20

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To cite this article: Junyan Feng, Ling Shan, Lin Du, Bing Wang, Honghua Li, Wei Wang, Tiantian Wang, Hanyu Dong, Xiaojing Yue, Zhida Xu, Wouter G. Staal & Feiyong Jia (2016): Clinical improvement following vitamin D3 supplementation in Autism Spectrum Disorder, Nutritional Neuroscience

To link to this article: http://dx.doi.org/10.1080/1028415X.2015.1123847

Published online: 22 Jan 2016.

Clinical improvement following vitamin D3 supplementation in Autism Spectrum Disorder

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Objective: High prevalence of vitamin D deficiency was previously reported in children with Autism Spectrum Disorder (ASD), but little is known about the efficacy of vitamin D3 treatment in ASD, although data from pilot studies seem promising. We hypothesized that serum vitamin D levels are reduced in ASD and correlate with the severity of disease. Also, we hypothesized that vitamin D3 treatment may be beneficial for a considerable portion of children with ASD.

Methods: In total, 215 children with ASD and 285 healthy control children were recruited in our study. Thirty seven of 215 ASD children received vitamin D3 treatment. The Autism Behaviour Checklist (ABC) and the Childhood Autism Rating Scale (CARS) were used to assess autism symptoms. High-performance liquid chromatography was used to assess the serum 25-hydroxyvitamin D [25(OH) D] level. Evaluations of ABC, CARS, and serum 25(OH) D levels were performed before and after 3 months of treatment.

Results: Serum levels of 25(OH) D were significantly lower in ASD children than typically developing children. Levels of serum 25(OH) D were negatively correlated with ABC total scores and language subscale scores. After vitamin D3 supplementation, symptom scores were significantly reduced on the CARS and ABC. In addition, the data also suggest that treatment effects were more pronounced in younger children with ASD.

Conclusion: Vitamin D deficiency might contribute to the aetiology of ASD. Supplementation of vitamin D3, which is a safe and cost-effective form of treatment, may significantly improve the outcome of some children with ASD, especially younger children (identifier ChiCTR-CCC-13004498).

Clinical Trial Registration: The trial 'Association of Polymorphisms of Vitamin D Metabolism-Related Genes With Autism and the Treatment of Autism with Vitamin D' has been registered at www.chictr.org/cn/proj/show.aspx? proj=6135 (identifier ChiCTR-CCC-13004498).

Keywords: Autism Spectrum Disorder, Vitamin D, Autism Behaviour Checklist, Childhood Autism Rating Scale

Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder characterized by social communication deficits and restricted, repetitive patterns of behaviour.[1] The prevalence of ASD has risen dramatically over the last several decades, from one in 5000 children in 1975 to one in 88 children in 2012, a 600% increase within 30 years.[2]

Although our understanding of the biology of ASD has impressively increased, the aetiology of ASD is largely unknown. Studies at different layers have shown the involvement of genetics, inflammation, autoimmune disorders, oxidative stress, neurotransmitters, and environmental factors.[3–9] At this point, there is a strong consensus that genetic factors play an essential role in ASD. Also, it has become apparent that environmental factors are involved,[3,4] which

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DOI 10.1080/1028415X.2015.1123847

probably interplay with genetic factors.[5–7] The hypothesis of gene–environment interaction, investigated for several other medical and psychiatric conditions, has been recently suggested for ASD as well. Within this framework, a putative role of vitamin D deficiency has been proposed.[5–12]

To date, several studies have found that vitamin D level was lower in ASD children than in healthy controls.[6,13–18] Trends of increased ASD prevalence in dark-skinned people, as well as a higher ASD risk in children of mothers with vitamin D deficiency during pregnancy have also been reported. Therefore, vitamin D deficiency during early childhood may be an important environmental risk factor for ASD.[19,20] We recently described a child with ASD, who suffered from vitamin D3 deficiency. This child clearly improved after vitamin D3 supplementation, suggesting that vitamin D might directly influence the core symptoms of autism.[21] Consistent with this finding, significant improvement was reported in a very recent study comparing vitamin D3 levels of 122 children with ASD and typically developing children.[22]

The clinical implication of these findings warrants further study. For instance, it could be that routine assessment of serum vitamin D level and adequate supplementation of vitamin D become part of the standard diagnosis and treatment procedures in ASD. However, at this point no consensus exists how to deal with this in the clinical practise. To further elucidate, the role of vitamin D in ASD we performed the present study, using the largest sample size to date.

Patients and methods

Subjects

Two hundred and fifteen ASD children from outpatient Department of Paediatric Neurology and Neuro-rehabilitation, The first Hospital of Jilin University, were recruited in this study. ASD diagnosis was made by paediatricians who have experience with the autism diagnostic observation schedule, according to the DSM-IV criteria of the American Psychiatric Association. The mean age of the ASD patients was 4.76 ± 0.95 years. Patients who had associated neurological diseases (such as cerebral palsy and tuberous sclerosis) and metabolic disorders (for example phenylketonuria) were excluded from this study. In total, 285 healthy controls (mean age of 5.12 ± 1.15 years) participated in our study. They were recruited from children activity centres in Changchun and matched with the ASD group in terms of age and sex. The participants did not receive any calcium and/or vitamin D therapy during the 6 months before joining our study. In addition, none of our subjects had a concomitant infection, photosensitivity or using photoprotection (such as broad-spectrum sunscreens) or treatment known to affect serum 25(OH) D levels (such as antiepileptic medication, corticosteroids, and other immunosuppressive drugs).Our study had lasted 6 months (April–September) in order to avoid seasonal influence on 25(OH) D level.

This study was approved by the Research Ethics Committee of First Hospital of Jilin University. Informed consent had been obtained from parents of all participants prior to their inclusion.

Method

The Autism Behaviour Checklist (ABC, score for normal children should be <53) and the Childhood Autism Rating Scale (CARS, score for normal children should be <30)[23,24] were used to assess autism symptoms. The serum 25(OH) D levels were assessed by the high-performance liquid chromatography. Serum 25(OH) D is considered to be adequate if it is ≥30 ng/mL, inadequate if it is between <30 and >10 ng/mL and deficient if it is ≤10 ng/mL.[14] All ASD children with vitamin D deficiency and vitamin D inadequacy were advised to receive vitamin D3 supplementation. Only 37 of 181 ASD children had finished 3 months of consistent vitamin D3 administration. Vitamin D3 was intramuscularly administered at a dosage of 150 000 IU per month (in total three injections) by a nurse, and orally administered at a dosage of 400 IU per day (in total 3months). Serum 25(OH) D levels were measured before and 3 months after treatment. In our study, assessment of the CARS was made by observing the behaviour of ASD children during child psychiatric examination, while evaluation of the ABC was performed by interviewing the parents. One rehabilitation doctor has conducted the evaluations of ABC and CARS both before and after 3months treatment.

Thirty seven ASD children who finished vitamin D supplementation were divided into two groups according to their age: early treatment group ($n = 20$) ≤3 years, later treatment group ($n = 17$) >3 years. The reduction of total ABC scores and total CARS scores was studied for both groups.

Statistical analysis

SPSS (Version 16.0) software was used for statistical analyses. The parametric data were presented as mean and standard deviation. *T*-test and Chi-square test were used to compare the differences between the two groups. Pearson's correlation test was used to evaluate relationships among continuous variables. An alpha value of 0.05 or below was accepted as the level of statistical significance.

Results

The demographic data of the study participants

In total, 215 ASD children and 285 healthy controls were recruited for this study (see Table 1). The mean

Table 1 The demographic data of ASD children and healthy controls

Parameters	ASD	Healthy control	*P*-value
Number of participants	215	285	
Age (years)	4.76 ± 0.95	5.12 ± 1.15	0.35
Sex			
Male (%)	173 (80.47)	225 (78.95)	0.45
Female (%)	42 (19.53)	60 (21.05)	0.36
Age of the mother at birth (years)	27.55 ± 1.13	26.54 ± 3.24	0.25
Age of the father at birth (years)	28.50 ± 1.87	28.13 ± 2.26	0.36
Gestational age (months)	38.89 ± 2.45	39.23 ± 1.25	0.32
Birth weight (kg)	3.44 ± 0.41	3.32 ± 0.21	0.42
Body weight (kg)	15.76 ± 0.23	16.33 ± 0.35	0.26
Height (cm)	107 ± 1.23	110 ± 1.35	0.35

Chi-square test and *T* test were used to check if there are differences between the two groups. Significant differences between the two groups were illustrated as $P < 0.05$.

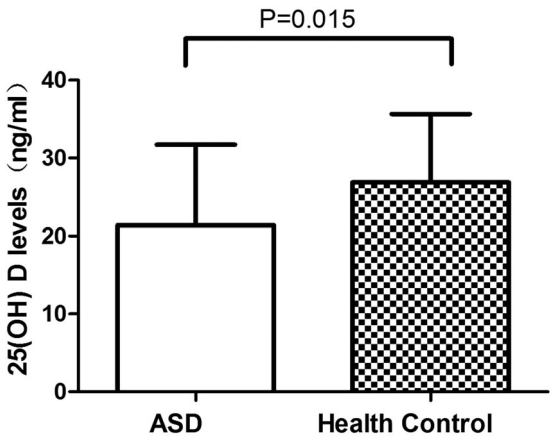

Figure 1 Serum 25(OH) D levels in ASD children and health control. *T*-test was used for the comparison.

age of the ASD children was 4.76 ± 0.95 years. Healthy controls (5.12 ± 1.15 years) were matched with the ASD group in terms of age and sex. Among ASD children, 80.47% ($n = 173$) was of male gender and 19.53% ($n = 42$) was of female gender, which is a ratio of approximately 4:1. No difference was found between the two groups concerning birth history (age of the mother at birth, age of the father at birth, gestational age, birth weight).

Serum 25(OH) D levels were lower in ASD children than healthy controls

The serum 25(OH) D levels were assessed by the high-performance liquid chromatography. ASD children had significantly lower serum levels of 25(OH) D than healthy controls (P=0.015, Fig. 1). There were, respectively, 13 and 71.2% being vitamin D deficient and vitamin D inadequate in the ASD group. Among healthy children, none were vitamin D deficient and 61.8% was vitamin D inadequate (Table 2). No significant difference was found in serum 25(OH) D levels between ASD boys and ASD girls.

We also examined the relationship between autism symptom scores (total and subscales of the ABC and CARS) and 25(OH) D levels in the ASD group. According to Pearson's correlation, 25(OH) D levels were negatively correlated with total ABC scores ($R^2 = 0.162$, P=0.018, Fig. 2A) and language scores of ABC subscale (Fig. 2B, $R^2 = 0.204$, P=0.003). No significant correlations were found between 25(OH) D levels and other ABC subscales, such as, for example, sensory, social skills, body and object use, social or self-help (P>0.05). CARS scores were not correlated with 25(OH) D levels (P>0.05).

Ameliorating behavioural abnormalities in ASD children after vitamin D3 supplementation

All ASD children with vitamin D deficiency and vitamin D inadequacy were advised to receive vitamin D3 supplementation, but only 37 of 181 ASD children finished 3months of consistent vitamin D3 administration (Table 3).This drop-out was caused by various reasons, such as travelling distance, or doubts about the efficacy of treatment. Parents of the ASD children who received vitamin D treatment, but who were unable to finish follow-up assessment, frequently reported symptom improvement of their children through a telephone interview. However,

Table 2 Vitamin D levels of all participants

Vitamin D levels	Autistic children ($n = 215$)	Health controls ($n = 285$)	*P*-value
Vitamin D deficiency (<10 ng/mL)	13% (28/215)	0	0.032
Vitamin D inadequacy (10–30 ng/mL)	71.2% (153/215)	61.8% (176/285)	0.028
Vitamin D adequacy (>30 ng/mL)	15.8% (34/215)	38.2% (109/285)	0.025

Chi-square test was used to check if there are differences between the two groups. Significant differences between the two groups are illustrated as $P < 0.05$.

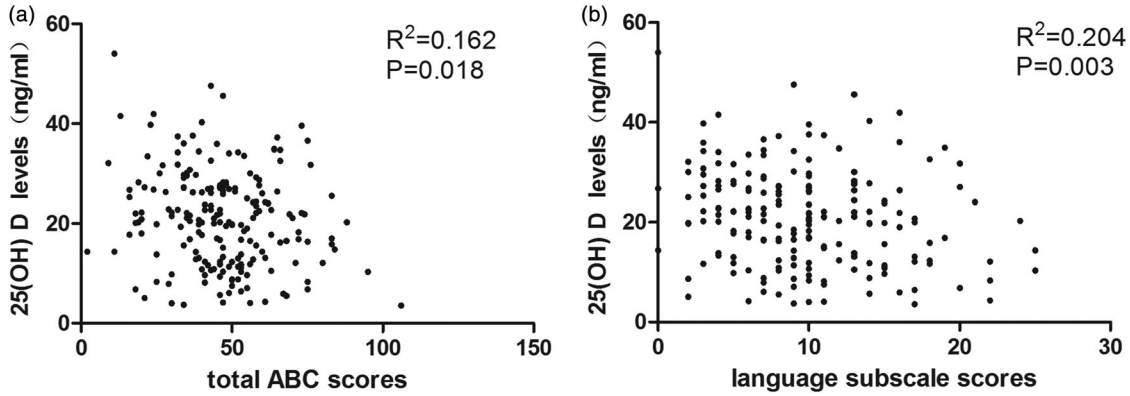

Figure 2 Correlation of 25(OH) D levels with total ABC scores and language scores of ABC subscale. Pearson's correlation test was used to evaluate relationships between 25(OH) D levels and ABC scores. (A) The correlation between 25(OH) D levels and total ABC scores. (B) The correlation between 25(OH) D levels and language scores of ABC subscale.

Table 3 Follow-up table of ASD children with Vitamin D deficiency and inadequacy

	Vitamin D deficiency (<10 ng/mL)	Vitamin D inadequacy (10–30 ng/mL)	Total number
Be advised to receive vitamin D supplementation	28	153	181
Taking vitamin D supplementation	26	68	94
Lost of contact or unable to conduct evaluations	6	51	57
Finished vitamin D supplementation	20	17	37

they were excluded from the analyses, because of incomplete data.

Vitamin D3 was intramuscularly administrated at a dosage of 150 000 IU every month and orally administered at a dosage of 400 IU every day. Evaluations (ABC, CARS, and serum 25(OH) D levels) were performed before and 3months after treatment. All patients showed clearly increased levels of serum 25(OH) D (P=0.000, Fig. 3A), after vitamin D supplementation. Also the total ABC scores, some scores of ABC subscales (social skills, body and object use, language, social or self-help), and total CARS scores were reduced significantly in comparison to the situation before treatment (P<0.05, Fig. 3B and D–H). Though sensory scores of ABC subscale demonstrated a decreasing trend after vitamin D treatment, no significant difference was found before and after treatment (P=0.185, Fig. 2C).

Vitamin D supplementation could be more effective in younger ASD children

Thirty seven ASD children who received vitamin D supplementation were divided into two groups according to their age: early treatment group (n = 20) ≤3 years, later treatment group (n = 17) >3 years. The reduction of total ABC scores and total CARS scores was studied for both groups. The reduction of total ABC scores (P=0.038, Fig. 4A) and total CARS scores (P=0.016, Fig. 4B) in early treatment group was more significant than in later treatment group. It may suggest that vitamin D supplementation could be more effective in younger ASD children.

Discussion

The main findings of this study are threefold. First, serum 25(OH) D levels were significantly lower in children with ASD compared with typical developing children. Second, serum 25(OH) D levels were independently associated with the clinical severity. Third, vitamin D3 supplementation improved clinical outcome, especially in the younger children with ASD.

Our main findings are in line with previous work showing decreased levels of vitamin D in ASD, increased ASD prevalence in dark-skinned people, and higher ASD risk in children of mothers with vitamin D deficiency during pregnancy.[6,13–20] The positive effects of vitamin D3 supplementation are also consistent with findings from a very recent study, and to the best of our knowledge this is the first replication of that finding.[22] Furthermore, we have also found that the reduction of total ABC scores and total CARS scores after vitamin D supplementation was more pronounced in younger ASD children (≤3 years). Because vitamin D also plays an important role in brain development,[25] this may not be surprising. The implication of this finding may be that vitamin D supplementation, in case of deficiency, should start as soon as possible.

Interestingly, 25(OH) D levels were negatively associated with total ABC scores and language scores of ABC subscale. This may suggest that lower

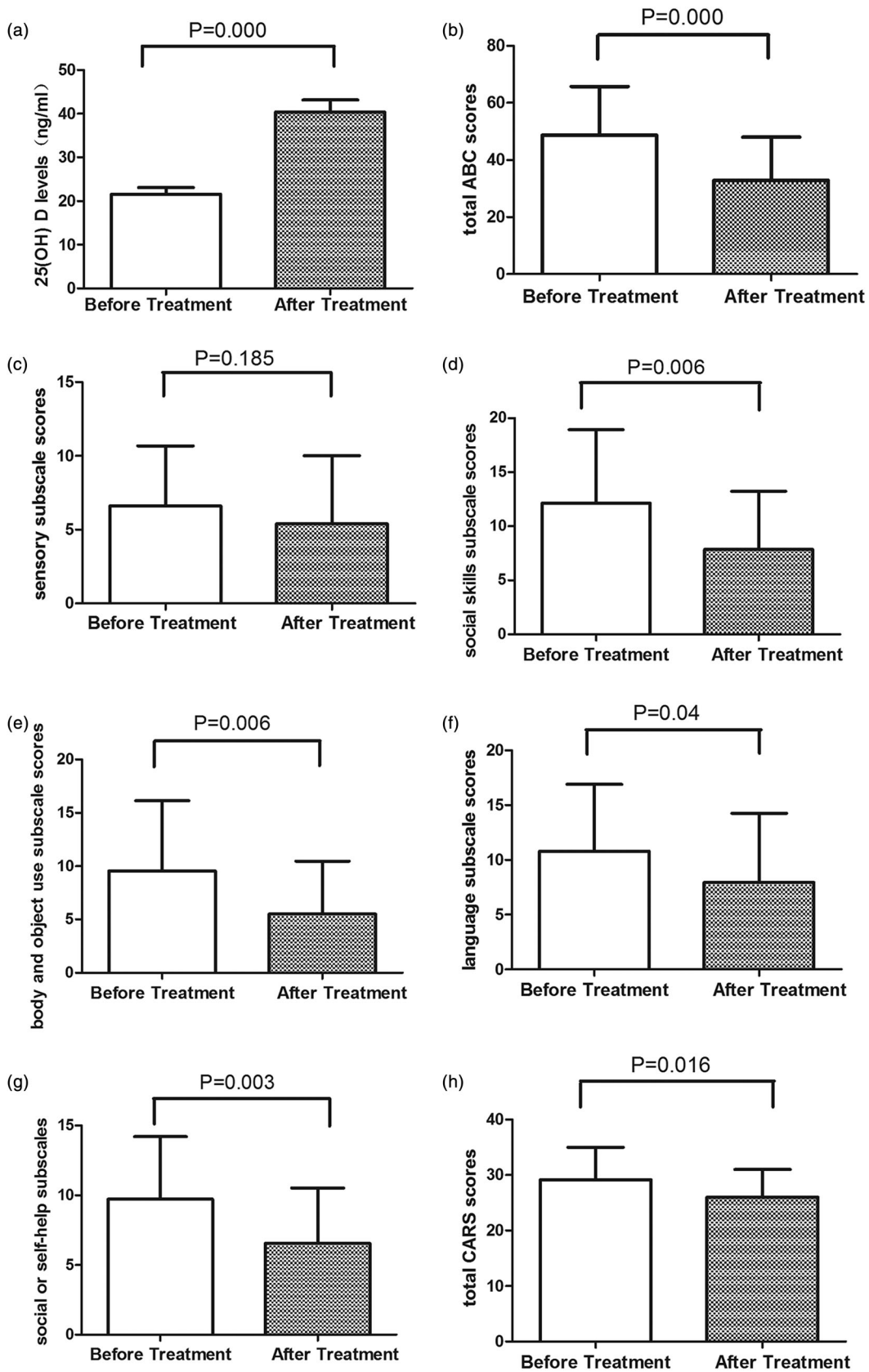

Figure 3 Changes of 25(OH) D levels and behavioural abnormalities in ASD children before and after treatment. *T*-test was used for the comparison. (A) Changes of 25(OH) D levels. (B) Changes of total ABC scores. (C) Score changes of sensory subscale (ABC). (D) Score changes of ABC subscale concerning social skills. (E) Score changes of ABC subscale concerning body and object use. (F) Score changes of language subscale (ABC). (G) Score changes of ABC subscale concerning social or self-help. (H) Changes of total CARS scores.

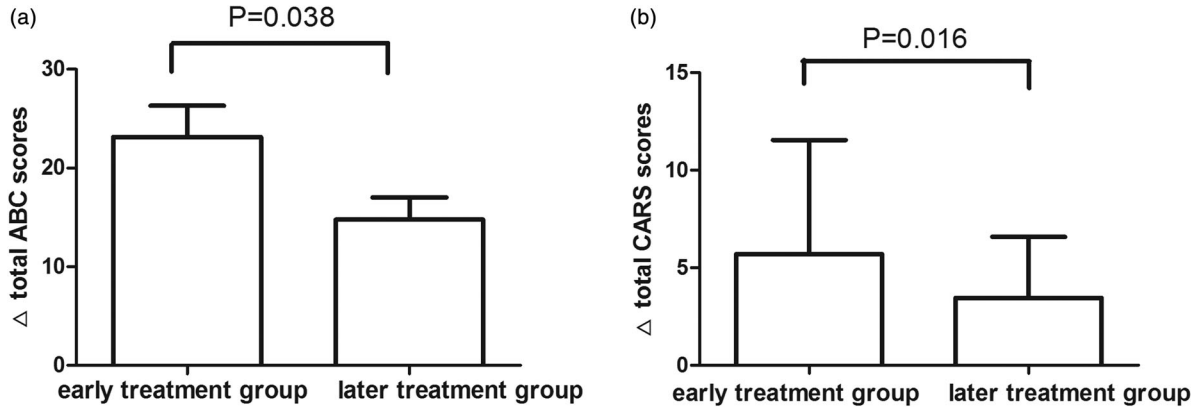

Figure 4 Reduction of total ABC scores and total CARS scores between early treatment group and later treatment group. *T*-test was used for the comparison. (A) Reduction of total ABC scores. (B) Reduction of total CAR scores.

serum 25(OH) D levels at inclusion were independently correlated with more severe clinical ASD symptoms. Mostafa and Al-Ayadhi[14] reported that serum 25(OH) D levels had a significant negative correlation with the CARS scores ($P<0.001$), which we could not confirm with our results. This may possibly be an effect of different rating methods, e.g. direct assessment of the child versus parental interview.

Vitamin D, whose main sources in human come from sun exposure and food intake, is well known to have several important functions. Vitamin D is regarded as a hormone that is active throughout our whole body, and not only important in regulating calcium and phosphate metabolism but also in neurodevelopment, immunological modulation (including the brain's immune system), antioxidation, anti-apoptosis, neural differentiation, and gene regulation.[25–28] As evidence has accumulated that vitamin D receptors are present in a wide variety of tissues, positive effects of vitamin D on the human body especially the brain have been well known for decades. Vitamin D deficiency has become a major health concern in our current society, possibly because of limited sun exposure for children, or changes in diet. Exact mechanism of the observed high prevalence of vitamin D deficiency in ASD is unclear, although it is tempting to suggest that diet and lack of sun exposure may play a role. Mostafa and Al-Ayadhi reported that vitamin D deficiency could be involved in the process of autoantibody production in patients with autism.[14] Patrick and Ames suggested that vitamin D deficiency may have pronounced effects on serotonin oxytocin and vasopressin concentrations in the brain.[29] Cannell[2] suggested that vitamin D may reduce the severity of autism symptoms through its anti-inflammatory actions, increasing T-regulatory cells and anti-autoimmune effects, and up-regulating glutathione a scavenger of oxidative by-products, therefore contributing to a decreased risk of autism. Even though all above-mentioned facts might be related to vitamin D deficiency, the mechanism of vitamin D deficiency in ASD children still needs to be further explored.

Our results are promising, but some considerations should be taken into account. First, many ASD children with inadequate serum vitamin D level refused to take vitamin D supplementation. Also, lots of ASD children did not finish 3 months treatment or contact was lost during follow-up period. Second, the sunlight exposure was not assessed in our work. Third, this study was not set up as a placebo controlled randomized clinical trial, and blind assessment was not performed.

Since vitamin D supplementation might directly improve the core symptoms of autism, possibly even more younger ASD children, we urge the field to perform randomly controlled and double blind clinical trials.

Conclusion

In this study, which is the largest to date, it is demonstrated that vitamin D deficiency might contribute to the aetiology of ASD. Supplementation of vitamin D3, which is a safe and cost-effective form of treatment, may significantly improve outcome in some children with ASD, especially in younger children. However, the exact mechanism how vitamin D contributes to the aetiology and treatment of ASD needs further study.

Disclaimer statements

Contributors Dr Feng drafted the initial manuscript; Drs Du and Shan collected the data for the article and critically reviewed the manuscript; Dr Bing Wang conducted the evaluations of ABC and CARS; Drs Li, Wei Wang, Tiantian Wang, Dong, and Yue diagnosed and recruited ASD children; Drs Xu and Staal carried out the initial analyses and reviewed and revised the manuscript; Dr Jia conceptualized and designed the study. And all authors approved the final manuscript as submitted.

Funding No funding was secured for this study.

Conflict of interest There is no conflict of interest for all authors.

Ethics approval This study was approved by the Research Ethics Committee of First Hospital of Jilin University.

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