Original Article

Iron and Vitamin D Levels among Autism Spectrum Disorders Children

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Abstract

Aim: The aim of this study was to investigate iron deficiency anemia and Vitamin D deficiency among autism children and to assess the importance of risk factors (determinants). **Subjects and Methods:** This was a case–control study conducted among children suffering from autism at the Hamad Medical Corporation in Qatar. A total of 308 cases and equal number of controls were enrolled. The Autism Diagnostic Observation Schedule-Generic was the instrument used for diagnosis of Autism. **Results:** The mean age (±standard deviation, in years) for autistic versus control children was 5.39 ± 1.66 versus 5.62 ± 1.81, respectively. The mean value of serum iron levels in autistic children was severely reduced and significantly lower than in control children (74.13 ± 21.61 μg/dL with a median 74 in autistic children 87.59 ± 23.36 μg/dL in controls) ($P = 0.003$). Similarly, the study revealed that Vitamin D deficiency was considerably more common among autistic children (18.79 ± 8.35 ng/mL) as compared to healthy children (22.18 ± 9.00 ng/mL) ($P = 0.004$). Finally, mean values of hemoglobin, ferritin, magnesium; potassium, calcium; phosphorous; glucose, alkaline phosphate, hematocrit, white blood cell, and mean corpuscular volume were all statistically significantly higher in healthy control children as compared to autistic children ($P < 0.001$). Multivariate logistic regression analysis revealed that serum iron deficiency, serum calcium levels, serum Vitamin D levels; ferritin, reduced physical activity; child order, body mass index percentiles, and parental consanguinity can all be considered strong predictors and major factors associated with autism spectrum disorders. **Conclusion:** This study suggests that deficiency of iron and Vitamin D as well as anemia were more common in autistic compared to control children.

Keywords: Autism spectrum disorders, epidemiology, ferritin, iron deficiency, risk factors, Vitamin D

Résumé

Objectif: L'objectif de cette étude était d'étudier l'anémie ferriprive et la carence en vitamine D parmi les enfants autistiques et d'évaluer l'importance des facteurs de risque (déterminants). **Sujets et méthodes:** il s'agissait d'une étude cas-témoins réalisée chez les enfants atteints d'autisme à la Hamad Medical Corporation au Qatar. Au total, 308 cas et un nombre égal de contrôles ont été inscrits. Le programme d'observation diagnostique de l'autisme générique (ADOS) était l'instrument utilisé pour diagnostiquer l'autisme. **Résultats:** L'âge moyen (± SD, en années) pour les enfants autistes versus témoins était de 5,39 ± 1,66 vs 5,62 ± 1,81. La valeur moyenne des taux de sérum dans les enfants autistes a été considérablement réduite et significativement plus faible que dans les enfants témoins (74,13 ± 21,61 ug/dL avec une médiane de 74 chez les enfants autistes 87,59 ± 23,36 ug/dL dans les témoins) ($P = 0,003$). De même, l'étude a révélé que la carence en vitamine D était considérablement plus fréquente chez les enfants autistes (18,79 ± 8,35 ng/mL) par rapport aux enfants en bonne santé (22,18 ± 9,00 ng/mL) ($P = 0,004$). Enfin, les valeurs moyennes de l'hémoglobine, de la ferritine, du magnésium; potassium calcium; phosphoreux; le glucose, le phosphate alcalin, l'hématocrite, le globule blanc (CMB) et le volume corpusculaire moyen [MCV] étaient statistiquement significativement plus élevés chez les enfants témoins sains que chez les enfants autistes ($P < 0,001$). L'analyse de régression logistique

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multivariée a révélé que la carence sérique en fer, les taux sériques de calcium, les taux sériques de vitamine D; ferritine, réduction de l'activité physique; l'ordre des enfants, les percentiles de l'IMC et la consanguinité parentale peuvent tous être considérés comme des prédicteurs forts et des facteurs majeurs associés aux troubles du spectre autistique. **Conclusion:** Cette étude suggère que la carence en fer et en vitamine D ainsi que l'anémie étaient plus fréquentes chez les enfants autistiques par rapport aux enfants témoins.

Mots-clés: Troubles du spectre de l'autisme, épidémiologie, ferritine, carence en fer, facteurs de risque, vitamine D

Introduction

Autism which has become a rather common disorder among 3–8 aged children may affect all aspects of a child's life.[1,2] Genetic, nutritional, and environmental factors have all been implicated as risk factors for autism.[3-8] Autism is a neurodevelopmental disorder characterized by severe qualitative impairments in social interaction, and verbal and nonverbal communication, along with restricted, stereotyped interests, and behaviors.[3] The disorder is accompanied by mental retardation in three out of four patients, and boys are four times more likely than girls to have the disorder. The underlying etiology is most likely multifactorial; and it is suggested that in most cases autism results from the interaction of multiple genetic and environmental factors.[1,2] As the risk of autism spectrum disorder (ASD) is generally acknowledged to reflect both genetic and environmental factors,[3-6] the interplay between genetic and environmental factors has become the subject of intensified research in the past several years.[3-9]

Iron deficiency is a major nutritional health concern among infants and young children resulting in insufficient iron to maintain normal cellular function. It affects 47% of children worldwide, 50% of children in developing countries,[3] and 6%–12% of children in developed countries.[9] An association between iron deficiency and autism has been documented.[10-15] Iron deficiency and iron deficiency anemia were more common in this clinical sample of children with global developmental delay and/or standard deviation (SD) than in the general population.[14,16] Vitamin D and iron have a unique role in brain homeostasis, embryogenesis and neurodevelopment, immunological modulation (including the brain's immune system), antioxidation, antiapoptosis, neural differentiation, and gene regulation.[17-23] Infants and children with ASDs often have food selectivity and restricted diets, putting them at risk for nutritional deficiencies.[9] The previous studies have demonstrated a high prevalence of iron deficiency in children with ASDs living in Wales, Canada, and Turkey.[7,11,12]

Although autism has a significant genetic component, it is primarily diagnosed through behavioral characteristics.[4-6] Diagnosing autism has been formalized with instruments carefully designed to measure impairments indicative of autism in three developmental areas: language and communication, reciprocal social interactions, and restricted or stereotypical interests and activities. One of the most widely used instruments is the Autism Diagnostic Observation Schedule (ADOS)-Generic ADOS.[6] The ADOS consists of a variety of semi-structured activities designed to measure social interaction, communication, play, and imaginative use of materials. The objective of this study was to investigate iron deficiency anemia and Vitamin D deficiency among autism children and to assess the importance of risk factors (determinants).

Subjects and Methods

This is a case–control study which was designed to determine the relationship between iron, anemia, Vitamin D, and autism in participants younger than 8-year-old at the Hamad Medical Corporation, Qatar. The survey was conducted from June 2011 to May 2014. This evaluation is based on 308 cases with ASDs and 308 control participants.

This study was approved by the Hamad General Hospital, Hamad Medical Corporation of Institutional Review Board Research Ethics Committee of and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All the persons who agreed to participate in this study gave their informed consent before their inclusion in the study.

Data collection

Study measurement-clinical evaluation of autistic patients

This was based on clinical history taken from caregivers, clinical examination, and neuropsychiatric assessment. In addition, the degree of the disease severity was assessed using the ADOS; an instrument for diagnosing and assessing autism based on specific coded behaviors that are included in a scoring algorithm using the Diagnostic and Statistical Manual of Mental Disorders Version # IV diagnostic criteria, resulting in a Communication score, a Reciprocal Social Interaction score, and a Total score.[6,16,17] The ADOS is an observation measure designed to assess reciprocal social interaction and communication, play, and use of imagination. The ADOS attempts to set a "social world" in which behaviors associated with ASDs can be observed through play, tasks, and conversation. The ADOS can be used to assist with educational planning.[6,16,17] The ADOS was originally developed to be used in conjunction with the Autism Diagnostic Interview.[6,8,10] This combination of instruments has been deemed the "gold standard" for the assessment of ASD.[6,8,10,16] The ADOS has been widely used in the research and academic centers for approximately 15 years to classify children with an ASD diagnosis for research studies and to assist in making clinical diagnoses. Published validity studies suggest good predictive validity, with sensitivities

ranging from 90% to 97%, and specificities ranging from 87% to 94% for autism/ASDs versus other clinical diagnoses.[6,8,16] The ADOS observation is run by a certified professional in a clinical environment and its duration can range from 30 to 60 min. Following the observation period, the administrator will then score the individual to determine their ADOS-based diagnosis, increasing the total time from observation through scoring to between 60 and 90 min in length.[6]

Autism participants aged younger than 8-year-old were identified from Pediatrics Clinics and School Health. As part of a cohort study, a random sample of 396 autism children was approached. Three hundred and eight participants gave consent and participated in the study; with a response rate of 77.8%. The study excluded the participants with following characteristics: calcium supplements or Vitamin D intake during the past 6 months before the study; history of epilepsy or antiepileptic drugs since they affect Vitamin D metabolism; any history of sun block use and the pubertal age around 10–11 since it is known that behavioral problems, and 25-hydroxyvitamin D2 (25OHD2) are affected by puberty and use of sun block.[8]

Selection of controls

Control participants younger than 8 years were identified from healthy participants who have not been diagnosed with ASD. This consisted of 405 participants who visited the primary health-care centers, of which only 308 participants were included with response rate of 76.0%. The healthy participants were selected after matching for the age, gender, and ethnicity of cases to give a good representative sample of the population studied.

Laboratory investigation

Blood collection and serum measurements of Vitamin D

Trained phlebotomists collected venous blood sample. The serum was separated and stored at 70°C until analysis. Serum 25OHD, a Vitamin D metabolite, was measured using a commercially available kit (DiaSorin Corporate Headquarter, Saluggia, Italy).[8] The samples were then assayed using competitive binding radioimmunoassay technique. Participants were classified into four categories: (1) severe Vitamin D deficiency, 25OHD <10 ng/ml; (2) moderate deficiency, 25OHD 10–19 ng/ml; (3) mild deficiency, 25OHD 20–29 ng/ml; and normal/optimal level is between 30 and 80 ng/ml.[17-22] Additional baseline biochemical parameters measured from the serum included Vitamin D in addition to calcium, phosphorus, magnesium, urea, parathyroid hormone, bilirubin, albumin, cholesterol, and triglycerides on the basis of the previous recommendations.[17-22]

We defined anemia as the state in which the hemoglobin concentration is 2 SDs lower than the mean hemoglobin concentration in the normal population of the same gender and age as defined by the WHO.[23,24] Based on this WHO report, anemia was defined as hemoglobin concentration <11.0 g/dL in children. Iron deficiency was diagnosed if ferritin was <12 μg/L for children aged between 6 and 60 months. In older children, iron deficiency was diagnosed by a ferritin level <15 μg/L or a ferritin level <30 μg/L in a child with C-reactive protein (CRP) (CRP blood test) ≥10 mg/L.[23,24]

Hematological Analysis was based on the instruction manual of the hematology analyzer (Sysmex Kx21). Total red blood cell (RBC) count, hemoglobin content (Hb; g/dL), hematocrit, total number of white blood cells (WBCs) lymphocyte (LYM) count LYM, LYM percentage, and platelet (PLT) count were assessed. In addition, mean corpuscular volume (MCV; fL), mean corpuscular hemoglobin (MCH; pg), MCH concentration, RBC distribution width (fL), PLT distribution width (fL), mean PLT volume (fL), and PLT larger cell ratio were also calculated.

The participants were interviewed by health professionals and nurses concerning their sociodemographic information such as age, gender, place of residence (urban and semi-urban), and family monthly income. Height and weight were measured using standardized methods. All participants wore light clothes and no shoes for this part of the examination.

Data are expressed as median, arithmetic mean, and standard deviation (SD) unless otherwise stated. Student's *t*-test was used to ascertain the significance of differences between mean values of two continuous variables and test confirmed by nonparametric Mann–Whitney test. Fisher's exact test (two-tailed) and Chi-square tests were performed to test for differences in proportions of categorical variables between two or more groups. Multivariate logistic regression analysis was used to assess the importance of risk factors (determinants) for autism. The level $P < 0.05$ was considered as the value for significance.

Results

Table 1 shows the sociodemographic characteristics of the studied autistic and healthy control children. The mean age (± SD, in years) of autistic versus control children was 5.39 ± 1.66 versus 5.62 ± 1.81. There were significant differences between autistic and control participants with respect to ethnicity ($P = 0.023$); higher educational level of the mother ($P = 0.011$); occupation of the mother ($P = 0.011$); higher monthly family income $P = 0.019$); higher consanguinity rate ($P = 0.008$); higher body mass index (BMI) ($P < 0.001$); less exposure to sun ($P = 0.045$); and less walking time per/day <60 min ($P = 0.003$).

Table 2 presents baseline chemistry biomarkers of autistic and control children. The mean values of serum iron in autistic children (74.1 ± 21.61 ug/dL) was significantly much lower than the normal value in the control children (87.59 ± 23.36 ug/dL) ($P = 0.003$). Similarly, the study revealed that mean serum Vitamin D level was considerably lower among autistic (18.8 ± 8.3 ng/ml) compared to healthy children (22.2 ± 9.0 ng/ml) ($P = 0.004$). In addition, mean values of hemoglobin, ferritin, magnesium, potassium, calcium, phosphorous, glucose, alkaline phosphate, hematocrit,

Table 1: Sociodemographic characteristics of studied participants with autism versus controls

Variables	Autism children (*n*=308), *n* (%)	Control children (*n*=308), *n* (%)	*P*
Age (mean±SD)	5.39±1.66	5.62±1.81	
Age group			
3-4 years old	91 (29.5)	92 (29.9)	0.906
5-6 years old	113 (36.7)	117 (39.0)	
7-8 years old	104 (33.8)	99 (32.1)	
Sex			
Male	153 (49.7)	137 (44.5)	0.170
Female	155 (50.3)	171 (55.5)	
Ethnicity of child			
Qatari	124 (40.3)	153 (49.7)	0.023
Non-Qatari/Arabs	184 (59.7)	155 (50.3)	
Educational level of father			
Illiterate	12 (3.9)	12 (3.9)	0.495
Primary	34 (11.0)	24 (7.8)	
Intermediate	46 (14.9)	45 (14.6)	
Secondary	109 (35.4)	102 (33.1)	
University and above	107 (34.7)	125 (40.6)	
Occupation of father			
Police/army/security	12 (3.9)	16 (5.2)	0.934
Sedentary/professional	109 (35.4)	110 (35.7)	
Clerk	32 (10.4)	33 (10.7)	
Businessman	77 (25.0)	71 (23.1)	
Government officer	78 (25.3)	78 (25.3)	
Educational level of mother			
Illiterate	33 (10.7)	43 (14.0)	0.011
Primary	51 (16.6)	59 (19.2)	
Intermediate	67 (21.8)	92 (29.9)	
Secondary	72 (23.4)	48 (15.6)	
University and above	85 (27.6)	66 (21.4)	
Occupation of mother			
Homemaker	103 (33.4)	95 (30.8)	0.011
Sedentary/professional	177 (25.6)	80 (26.0)	
Clerk	55 (17.9)	84 (27.3)	
Business woman	73 (23.7)	49 (15.9)	
Monthly income ($US dollars)			0.019
<$3000	77 (28.0)	102 (33.1)	
$3000-$6000	123 (39.4)	125 (40.6)	
>$6000	108 (32.7)	81 (26.3)	
BMI group			
<85th percentile	248 (89.4)	255 (80.3)	<0.001
85th-95th percentile	39 (8.7)	34 (16.1)	
>95th percentile	21 (2.0)	15 (3.5)	
Consanguinity			
Yes	118 (38.3)	87 (28.2)	0.008
No	190 (61.7)	221 (71.8)	
Exposure to sun			
Yes	102 (33.1)	126 (40.9)	0.045
No	206 (66.9)	182 (59.1)	
Walking time per/day <60 min			
Yes	110 (35.7)	142 (46.1)	0.003
No	208 (67.5)	166 (53.9)	

BMI=Body mass index, SD=Standard deviation

WBC, and MCV were all statistically significantly higher in healthy controls compared to autistic children ($P < 0.001$).

Table 3 identified potential risk factors for ASDs in children: serum iron deficiency (odds ratio [OR] = 2.83; confidence interval [CI] 1.81–4.72 $P < 0.001$); serum calcium level (OR = 2.74;CI 1.65–4.81, $P < 0.001$); serum Vitamin D level (OR = 2.36; CI 1.74–3.44, $P = 0.002$); ferritin (OR = 2.45;1.86–3.93; $P = 0.004$); less physical activity (OR = 2.51;1.63–4.67; child order (OR = 1.68;1.42–3.36; $P = 0.019$), BMI (OR = 2.39; CI 1.54–3.78, $P = 0.028$); and parental consanguinity (OR = 1.73; CI 1.48–2.65, $P = 0.046$) were considered as strong predictors and main factors associated with ASDs after adjusting for age, gender, and other variables.

Discussion

This case–control study presents, to the best of our knowledge, the first report on an establishing level of iron deficiency in children with autism in Qatar and in Arabian Gulf Countries. Despite many studies, the epigenetics of iron deficiency are also still not well understood.[9,10,12,15] These results indicate a significant low mean value of iron deficiency in children with ASDs. The mean values of iron deficiency and Vitamin D deficiency reported in this study are significantly lower in comparison with other reported studies.[3,6,10-15] Our findings confirmed that iron deficiency and anemia are common in autism, in parallel with the previous reports.[4,8,12,15]

Iron deficiency is reported to be the most prevalent nutritional problem among children in the world today,[10-16,25] and there is considerable evidence that iron is important for neurological functioning and development.[20-22] For the first time, this study demonstrated abnormally low serum ferritin levels in children with autism in Arabian Gulf Countries. Serum ferritin levels were very low in children with autism compared to controls, this is consistent with the previous reported studies.[10-15] The previous studies have revealed that iron deficiency was associated with autism and the current study revealed an increased risk of autism was noted among those with iron deficiency anemia, which was compatible with this report.[7,10-13]

As it is the case for most iron-deficient children in the general population,[12-15] iron deficiency in autism may be a result of reduced dietary iron intake. Children with autism often have very restricted food preferences due to smell, taste, texture, or other characteristics of the foods.[7,12-13] Several studies[10-15] showed

Table 2: Clinical biochemistry baseline value of participants with autism versus controls

Variables	Reference normal value	Mean±SD		*P*
		Autism (*n*=308)	Controls (*n*=308)	
Vitamin D (ng/ml)	30-80	18.79±8.35	22.18±9.00	0.004
Serum iron (ug/dL)	37-158	74.13±21.61	87.59±23.36	0.003
Ferritin (ng/ml)	15-150	36.57±5.12	38.49±5.73	<0.001
Hemoglobin (g/dL)	10.5-12.7	12.03±2.13	12.86±2.02	<0.001
Magnesium (mmol/L)	0.65-1.05	0.826±0.07	0.884±0.06	<0.001
Potassium (mmol/L)	3.4-4.7	4.252±0.50	4.575±0.55	<0.001
Calcium (mmol/L)	2.10-2.5	2.09±0.12	2.39±0.14	<0.001
Phosphorous (mmol/L)	0.4-1.3	1.362±0.31	1.553±0.28	<0.001
Glucose (mmol/L)	4-6	4.65±0.4	4.35±0.9	<0.001
Alkaline phosphate (U/L)	149-401	268.36±92.6	215.22±84.6	<0.001
Hematocrit	36%-46%	36.32±2.81	39.07±2.66	<0.001
White blood cells ($\times 10^3$/ul)	5.3-11.5	9.74±3.56	10.93±3.66	<0.001
MCV (fL)	80-96	77.23±5.92	85.24±6.53	<0.001

MCV=Mean corpuscular volume, SD=Standard deviation

Table 3: Multivariate logistic regression analysis potential risk factors for autism disorder

Independent variables	OR	95% CI	*P*
Serum iron deficiency (ug/dL)	2.83	1.81-4.72	<0.001
Serum calcium level (mmol/L)	2.74	1.65-4.81	<0.001
Vitamin D deficiency (ng/ml)	2.36	1.74-3.44	0.002
Ferritin (ng/ml)	2.45	1.86-3.93	0.004
Less physical activity	2.51	1.63-4.67	0.005
Child order	1.68	1.42-3.36	0.019
BMI in percentiles	2.39	1.54-3.78	0.028
Consanguinity	1.73	1.48-2.65	0.034

OR=Odds ratio, CI=Confidence interval, BMI=Body mass index

that nearly half of children with autism had an inadequate intake of dietary iron. In addition, Dosman *et al*.[7-13] reported that twice as many preschoolers (69%) than school-aged children (35%) had an insufficient intake of dietary iron. Furthermore, Xia *et al*.[26] found that intake of iron increased with age in 2–9-year-old children with autism. Because younger children with autism are more selective about what they eat, iron deficiency may be more prevalent in this age group.

A great deal of evidence has shown that iron is an important component in cognitive, sensori motor, and social-emotional development and functioning because the development of central nervous system processes is highly dependent on iron-containing enzymes and proteins.[27,28] Iron deficiency increased the risk of psychiatric disorders, including mood disorders, ASD, attention deficit hyperactivity disorder, and developmental disorders.[21] Deficiency of iron in early life may increase the risk of psychiatric morbidity. Our findings confirmed that iron deficiency and Vitamin D are common in autism, in parallel with the previous reports.[4,8,12,15,27,28]

Limitations of study

Although our study included a large sample of participants and is case–controlled, it has some limitations. Our study was limited by the content of existing repositories that, for reasons related to the recruitment processes of those studies, contain very few individuals who did not meet the criteria for an autism classification. Data on the possible maternal iron deficiency and anemia before and after delivery are lacking. Another limitation is the iron source. This study did not include data on children kept on avoidance/restriction diets. It is known that avoidance or restriction diets are one of the modalities of therapy for some patients with autism. Data on duration of outdoor activity are lacking, another limitation in our study.

Conclusion

The current studies confirm that deficiencies of iron and Vitamin D and anemia were higher in autistic compared to control children. The results suggest that serum ferritin levels should be monitored in every case of autism as a part of baseline investigation.

What's known on this

The studies strongly suggest that iron deficiency is linked to brain dysfunction. However, data are lacking with regards to the association between iron deficiency and autism.

What this study adds

The association between deficiencies of iron and Vitamin D and autism in young children and associated risk factors has never been reported in the literature. Perhaps, this is the first study to investigate an association between circulating levels of iron and autism among a highly endogamous population. The present study revealed that Vitamin D deficiency was also higher in autistic compared to healthy children. Supplementing infants with iron and Vitamin D might be a safe and effective strategy for reducing the risk of autism.

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Conflicts of interest

There are no conflicts of interest.

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