Association of Brain Derived Neurotrophic Factor with Iron as well as Vitamin D, Folate and Cobalamin in Pediatric Metabolic Syndrome

Mustafa M. Donma, Orkide Donma

Abstract**—**The impact of metabolic syndrome (MetS) on cognition and functions of the brain is being investigated. Iron deficiency and deficiencies of B9 (folate) as well as B12 (cobalamin) vitamins are best-known nutritional anemias. They are associated with cognitive disorders and learning difficulties. The antidepressant effects of vitamin D are known and the deficiency state affects mental functions negatively. The aim of this study is to investigate possible correlations of MetS with serum brain-derived neurotrophic factor (BDNF), iron, folate, cobalamin and vitamin D in pediatric patients. 30 children, whose age- and sex-dependent body mass index (BMI) percentiles vary between 85 and 15, 60 morbid obese children with above 99^{th} percentiles constituted the study population. Anthropometric measurements were taken. BMI values were calculated. Age- and sex-dependent BMI percentile values were obtained using the appropriate tables prepared by the World Health Organization (WHO). Obesity classification was performed according to WHO criteria. Those with MetS were evaluated according to MetS criteria. Serum BDNF was determined by enzyme-linked immunosorbent assay. Serum folate was analyzed by an immunoassay analyzer. Serum cobalamin concentrations were measured using electrochemiluminescence immunoassay. Vitamin D status was determined by the measurement of 25-hydroxycholecalciferol [25-hydroxy vitamin D3, 25(OH)D] using high performance liquid chromatography. Statistical evaluations were performed using SPSS for Windows, version 16. The p values less than 0.05 were accepted as statistically significant. Although statistically insignificant, lower folate and cobalamin values were found in MO children compared to those observed for children with normal BMI. For iron and BDNF values, no alterations were detected among the groups. Significantly decreased vitamin D concentrations were noted in MO children with MetS in comparison with those in children with normal BMI ($p \leq 0.05$). The positive correlation observed between iron and BDNF in normal-BMI group was not found in two MO groups. In THE MetS group, the partial correlation among iron, BDNF, folate, cobalamin, vitamin D controlling for waist circumference and BMI was $r = -0.501$; $p \leq 0.05$. None was calculated in MO and normal BMI groups. In conclusion, vitamin D should also be considered during the assessment of pediatric MetS. Waist circumference and BMI should collectively be evaluated during the evaluation of MetS in children. Within this context, BDNF appears to be a key biochemical parameter during the examination of obesity degree in terms of mental functions, cognition and learning capacity. The association observed between iron and BDNF in children with normal BMI was not detected in MO groups possibly due to development of inflammation and other obesity-related pathologies. It was suggested that this finding may contribute to mental function impairments commonly observed among obese children.

Keywords**—**Brain-derived neurotrophic factor, iron, Vitamin B9, Vitamin B12, Vitamin D.

Mustafa M. Donma is with the Namik Kemal University, Faculty of Medicine, Department of Pediatrics, Tekirdag, Turkey (corresponding author, phone: 00-90-532-371-72-07; fax: 00-90-282-250-99-28; e-mail: mdonma@gmail.com).

Orkide Donma is with the Istanbul University Cerrahpasa, Cerrahpasa Medical Faculty, Department of Medical Biochemistry, Istanbul, Turkey (e-mail: odonma@gmail.com).

I. INTRODUCTION

IRON is an indispensable parameter for brain functions. Iron deficiency anemia is one of the most common diseases among the pediatric population. The role of iron in obesity-related pathogenesis is also well-documented. Obesity is a growing health problem during the childhood years in the present age. Its relation with many chronic and severe diseases is well-established [1]-[4]. MetS is one of such diseases. This syndrome is characterized by previously defined components. Central, obesity is the component in the first place of this list.

Aside from iron, some other micronutrients such as folate and cobalamin also participate in cognition. As an important consequence of their deficiencies, nutritional anemia emerges. The status of these vitamins has been investigated also in obesity [5]-[7].

Vitamin D, so far, has been well-known for its participation in calcium and phosphorus metabolisms. Recently its significance has also been reported for the prevention of depressive disorders. Higher vitamin D levels are associated with better attentional functions. Deficiency of this vitamin has already been reported during obesity. Mental functions are also affected by the deficiency of vitamin D. Depressive disorders, learning difficulties, cognitive problems can be listed within the scope of obesity-related problems [8]-[11].

BDNF may play important roles in the development and pathophysiology of childhood obesity [12]-[15]. Its concentration has also been investigated in patients with bipolar mania [16]. Its association with iron metabolism lies at the center of this discussion. There are many studies linking BDNF levels with iron concentrations. Generally, the deficiency of BDNF is associated with iron deficiency states and impaired cognitive functions [17], [18]. The interrelationship of MetS and neurodegenerative diseases with focus on BDNF is also emphasized [19].

The aim of this study was to investigate possible relations among BDNF, folate, cobalamin, vitamin D and iron in morbid obese children and those with MetS in case of normal iron homeostasis.

II. Patients and Methods

A. Patients

A total of 90 children participated in this study. Ages of the study population were varying between 5.1 years and 16.2 years. The study protocol was approved by the institutional ethics committee. Written informed consent forms were taken from the parents of the children.

B. Anthropometric Measurements

Height, weight, waist circumference (WC) and hip circumference (HC) of the individuals were recorded. BMI and WC-to-HC values were calculated.

C. Obesity Classification

Morbid obese children were selected according to WHO criteria [20]. Children, whose age- and sex-adjusted BMI percentiles were above 99, were included in morbidly obese group. These children were divided into two groups; being with and without MetS criteria.

D. Definition of MetS Components

MetS components were determined [21]. Central obesity was the main component. Fasting blood glucose (FBG) above 100 mg/dl, systolic and diastolic blood pressure values above 130 mm. Hg and 85 mm. Hg, respectively, and triacylglycerol concentrations above 150 mg/dl or high density lipoprotein cholesterol levels below 40 mg/dl were the other criteria to select children, who will constitute MetS group.

E. Laboratory Determination of Biochemical Parameters

Enzyme-linked immunosorbent assay was used for the determination of serum BDNF concentrations. Serum folate and cobalamin concentrations were analyzed using an immunoassay analyzer and electrochemiluminescence immunoassay. Value for vitamin B12 ≤ 147 and 148-221 pmol/L were accepted as low and borderline, respectively. Vitamin B9 levels ≤4 mcrg/L defined deficiency state. Determination of vitamin D status was performed by high performance liquid chromatography. Vitamin D status was introduced as 25-hydroxycholecalciferol [25-hydroxy vitamin D3, 25(OH)] concentrations measured. Values < 20 ng/ml were defined as vitamin D deficient.

F. Statistical Evaluation

The statistical package program SPSS was used. Within the scope of descriptive statistics, median, mean±SD (SEM) values were calculated for anthropometric measurements as well as biochemical parameters. Bivariate and partial correlation analyses were performed. Linear regression lines were drawn. p values less than 0.05 were accepted as statistically significant.

III. Results

Thirty children with normal-BMI (Group 1), 30 MO children (Group 2) and 30 children with MetS (Group 3) participated in the study. The mean ± SD (SEM) values for ages of the groups 1, 2 and 3 were 120.4 ± 35.8 (6.5), 120.0 ± 10.7 (2.0), and 119.0 ± 30.2 (5.7) months, respectively. Anthropometric measurements and some obesity-related ratios were shown in Table I.

TABLE I
WC and WC as Well as BMI And Waist-To-Hip Ratio Values Of The Study Groups

Parameter	Group1	Group 2	Group 3
BMI (kg/m^2)	17.0±2.3 (0.4)	26.9±2.3 (0.4)	28.8±5.5 (1.1)
WC (cm)	61.2±8.9 (1.6)	86.9±6.9 (1.3)	96.0±22.5 (4.3)
HC (cm)	75.1±12.2 (2.2)	95.5±6.2 (1.1)	100.2±14.2 (2.7)
WC/HC	0.82±0.06 (0.01)	0.91±0.05 (0.01)	0.96±0.19 (0.04)

WC/HC= waist-to-hip circumference ratio, Group 1= N-BMI, Group 2= morbid obese, Group 3= MetS.
[$BMI^{1\text{-}2\ <0.001,\ 1\text{-}3\ <0.001}$, $WC^{1\text{-}2\ <0.001,\ 1\text{-}3\ <0.001,\ 2\text{-}3\ <0.05}$, $HC^{1\text{-}2\ <0.001,\ 1\text{-}3\ <0.001}$, $WC/HC^{1\text{-}2\ <0.001,\ 1\text{-}3\ <0.001}$]

Statistically significant increases were observed in Group 2 and Group 3 compared to the values obtained for Group 1. WC values differed significantly also between Group 2 and Group 3.

Mean±SD (SEM) values of BDNF and micronutrient concentrations of the groups were given in Table II.

TABLE II
BDNF, iron, folate, cobalamin and vitamin D concentrations of the study groups

Parameter	Group1	Group2	Group 3
BDNF (pg/ml)	7.12	6.31	7.51
Iron (μg/dl)	88.8±43.8 (8.0)	73.9±31.2 (5.7)	69.7± 31.2 (5.9)
Folate (μg/L)	8.5±3.8(0.7)	7.6±2.7(0.5)	6.7±2.7(0.5)
Cobalamin (pmol/L)	424±166(30)	381±127(23)	342±136(26)
Vitamin D (ng/ml)	27.4±10.5(2.3)	22.1±11.2(2.6)	19.0±10.0(2.2)

Group 1= N-BMI, Group 2= morbid obese, Group 3= MetS.
[$BDNF^{NS}$, $iron^{NS}$, $folate^{NS}$, $cobalamin^{NS}$, $vitamin\ D^{1\text{-}3\ <0.05}$]

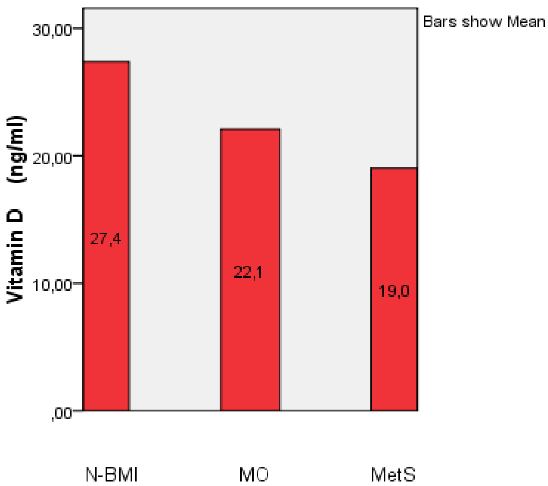

Fig. 1 Vitamin D concentrations in children with normal body mass index (N-BMI), morbid obesity (MO) and MetS

As going from Group 1 to Group 3, in parallel with the increase in obesity degree, decreased iron, folate and cobalamin concentrations were observed. However, these decreases were not statistically significant (p > 0.05). On the other hand, upon evaluation of vitamin D concentrations, a statistically significant decrease was found in MetS group in comparison with those in Group with N-BMI (Fig. 1).

Bivariate correlation analysis showed a positive correlation between BDNF and iron levels (r = 0.352; p = 0.05) in Group 1 (Fig. 2).

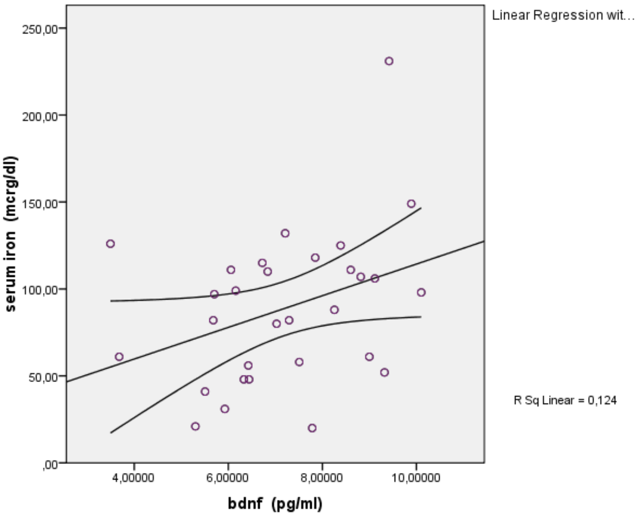

Fig. 2 Bivariate correlation between serum iron and BDNF concentrations in children with N-BMI (Linear Regression wit… = Linear Regression with 95.0% Mean Prediction Interval)

No correlation existed between these two parameters in MO and MetS groups.

Partial correlation analyses showed a negative correlation between vitamin D and cobalamin, when iron, BDNF, folate, cobalamin, vitamin D controlling for WC and BMI (r = -0.501; p = 0.029) in MetS group (Fig. 3). This correlation could not be detected in MO or N-BMI group.

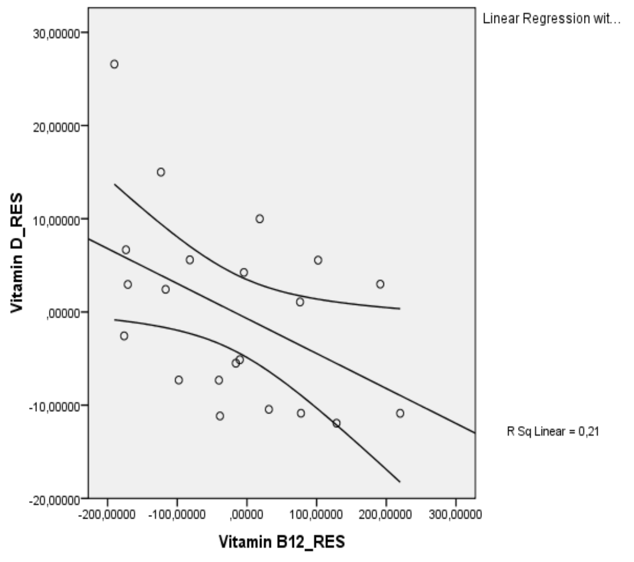

Fig. 3 Partial correlation between vitamin D and cobalamin in MetS group (Linear Regression wit… = Linear Regression with 95.0% Mean Prediction Interval)

Any correlation was not detected when the parameters were evaluated for WC-to-HC ratio.

IV. Discussion

Memory decline, uncontrolled inflammation, decreased cognitive capacity as well as increased oxidative stress, which are observed in MetS may lead to mental disorders and age-related clinical states such as neurodegenerative diseases based upon impaired BDNF status [19]. In our study, the positive correlation observed between iron and BDNF in the N-BMI group was the indicator of this close association between these two brain-related parameters. Some interfering events may contribute to the lack of such association in MO as well as MetS groups.

The study population was composed of children with normal iron status, not deficient. Being an interesting aspect of this study, this may be another supportive aspect of this finding and may also indicate the protective effect of iron for brain functions.

Our findings showed that any correlation could not be detected between WC or BMI and the other biochemical parameters when WC or BMI alone was taken into consideration. When both of these obesity parameters were evaluated together, a statistically significant correlation was detected. This finding pointed out that both WC as well as BMI should collectively be handled during the evaluation of obesity.

Iron deficiency causing microcytic anemia leads to learning difficulties in children. Also, deficiencies of folate and cobalamin, collectively or alone cause megaloblastic macrocytic anemia, which leads to problems related to cognitive disorders. Although vitamin D, in the first instance, appears as a vitamin, which is related to bone development, deficiency states of this vitamin may impact mental functions improperly [11], [22], [23].

Under normal circumstances, vitamin D deficiency is associated with MetS in MO [24]. Also in our study, vitamin D levels were significantly decreased in the MetS group. Our results related to vitamin B_{12} and B_9 levels were also lower in children with MetS, but decreases were insignificant. Deficiency percentages of vitamin D and B_9 were 48% and 3.6%, respectively. There was no deficient case in terms of vitamin B_{12} concentrations. The percentage of borderline cases was 26%. However, there are some controversial findings related to vitamin D as well as cobalamin status in terms of breast cancer. Unexpectedly, associations of increased breast cancer risk with higher vitamin D and vitamin B12 concentrations were reported [25]-[27].

In this study, there was no correlation between WC or BMI and iron, vitamin D, cobalamin or folate. On the other hand, when BDNF is added to these four micronutrients and then correlations of them with WC and BMI together were investigated, a correlation was detected between vitamin D and cobalamin in the MetS group. In spite of the decreased levels of both parameters in this group, the negative direction of this association is also an unexpected finding as in the above examples. This may be due to the intense vitamin D deficiency against the lack of deficiency in terms of vitamin B12 status. Based upon these findings, BDNF appears to be a main biochemical parameter upon evaluation of obesity degree as well as mental function and cognitive/learning capacity. In such studies, it is quite important to consider also BDNF in addition to routine biochemical parameters from the evaluation of child's mental status point of view.

In this study, the significant correlation observed between iron and BDNF in healthy children disappeared in MO and MetS groups due to the development of inflammation and the other related pathologies. It was suggested that this finding may contribute to mental function problems observed in obese children.

The significant difference observed between N-BMI and MetS in terms of vitamin D suggested that vitamin D should also be considered aside from iron, folate and cobalamin for the evaluation of the clinical problems such as cognitive disorders or depression.

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