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Brain Derived Neurotrophic Factor and Serotonin Levels in Autistic Children: Do They Differ in Obesity?

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Abstract

BACKGROUND: The risk of obesity among autism spectrum disorder (ASD) children is high which could be related to a disorder in their metabolism. Brain derived neurotrophic factor (BDNF) is involved in metabolic control, language behavior, and intellectual development. Serotonin has a role in satiety and energy expenditure.

AIM: Therefore, the aim of this study was to measure the serum levels of BDNF and serotonin in obese compared to non-obese ASD children. The influence of obesity on ASD severity, intellectual, and language development was also investigated.

METHODS: The study included 60 autistic children (Group I: 30 ASD children with obesity and Group II: 30 ASD children without obesity). The serum BDNF and serotonin levels were estimated by ELISA and by high-performance liquid chromatography.

RESULTS: All participants manifested delayed language development. Almost all of them had intellectual disability. The difference between groups regarding ASD severity, language, and intellectual development was non-significant. However, BDNF level in obese group was less than that in the other group while serotonin was higher in the obese group with significant statistical difference.

CONCLUSION: The difference between the groups regarding the levels of BDNF and serotonin, which are involved in the brain development, could be related to obesity. The influence of obesity on ASD severity, intellectual, and language development of ASD children was not distinctive in the participants. The influence of such markers on ASD severity and cognitive performance needs further investigations.

Introduction

The prevalence of obesity in children with autism spectrum disorder (ASD) has been reported to be more than that in general population. It was estimated to range between 17% and 32% in ASD children. Individuals with ASD have risk factors which make them more susceptible to weight gain. They manifest feeding disorders such as food selectivity which is commonly for high caloric and low-nutritive kind. Decreased micronutrients intake would lead to high fat deposition in their bodies. Food is also used as reinforcement for autistic children to encourage good behavior [1]. Sedentary lifestyle and some medications such as second generation antipsychotics are also involved in increasing obesity risk. There have been links between obesity and some genetic changes in ASD (e.g., microdeletions of chromosomes 11 and 16) [2]. Furthermore, low socioeconomic status, sleep disorder, hormonal imbalance, gastrointestinal disturbances, and reduced gut microbiota in ASD individuals could play a role in such problem [3].

Changes in the neuroanatomical features of individuals with ASD (either obese or non-obese) have been suggested to be involved in ASD pathogenesis. Children with ASD manifested change in the volume of hypothalamus, amygdala, fornix, hippocampus, and aberrant connections between these areas and other brain areas [4], [5], [6]. Therefore, neurotransmitters responsible for brain functioning in these areas (e.g., brain derived neurotrophic factor [BDNF] and serotonin) were suspected to be altered in the brain and body of such individuals. The levels of BDNF and serotonin (5-HT) have been reported to be altered in ASD. The BDNF was reported to be elevated in ASD children while less than normal in newborns who later develop ASD [7], [8], [9]. The level of blood serotonin was reported to be elevated in 25–60% of autistic individuals and was linked to familial elevation of 5-HT levels [10], [11]. However, it did not differ in ASD population from normal controls in other studies [12], [13]. It is worth noting that BDNF can cross the blood–brain barrier yet the peripheral serotonin cannot. Thus, brain serotonin could be involved in the pathogenesis of ASD in spite of not differing in its

level in peripheral blood. On the other hand, peripheral serotonin could be involved in ASD pathogenesis through its role in controlling gut functioning which was reported to be disturbed in ASD [14].

BDNF is essential for connectivity between synapses in brain and peripheral nervous system. It facilitates neuronal growth and supports survival of neurons [15]. It is involved in long-term potentiation which is related to long-term memory. BDNF was reported to be related to serotonergic brain neurons in animal studies [16]. Hypothalamic BDNF was found to be responsible for energy homeostasis and modulation of food intake. Abnormalities of BDNF gene which lead to reduction of BDNF level were associated with hyperphagia and obesity in human and animal models. Besides, administration of BDNF was found to lead to reduction of insulin resistance and induction of weight loss which suggests the role of BDNF as a metabotropic factor [17].

Serotonin serves as a neurotransmitter and an intermediate substrate for melatonin synthesis. It was found to be involved in sensory brain development in animal studies [13]. It regulates behavior and it has a role in appetite suppression, and promotion of energy expenditure which is achieved by facilitating sympathetic drive to brown adipose tissue. The gastrointestinal tract is the main source of peripheral 5-HT. Peripheral serotonin has a role in enhancing nutrient absorption and storage. Fatty acids and glucose stimulate the release of serotonin from the duodenum which promotes gut peristalsis and nutrient absorption [18].

In addition to social and behavioral disorders, children with ASD manifest delayed language development. It is the most common presenting symptom for such children. A large percentage of them manifest intellectual disability as well [19]. Obesity was reported to increase the risk of type 2 diabetes, sleep apnea, orthopedic disorders, hypertension, and dyslipidemia [20]. However, the influence of obesity on language and intellectual development and on severity of ASD in autistic children was not adequately investigated. The process of rehabilitation of autistic children is quite challenging and having comorbid obesity increases the health risks and adds more burdens on the family and the health system especially in developing countries. Investigating possible markers of obesity in such children are essential in the process of their management. This will be beneficial to verify the relation or contribution of such markers to obesity and would participate in protecting autistic children from developing obesity and would help in proper management of such children and in reducing health hazards that are related to obesity. Therefore, the aim of this study was to verify the presence of a difference between obese and non-obese autistic children regarding the serum levels of BDNF and serotonin. The influence of obesity on the severity of ASD, the development of intellectual functioning and language abilities was also investigated.

Subjects and Methods

The study was conducted on 60 ASD children: 30 autistic children with obesity in Group I (6.2 ± 1.4; 26 males and four females) and 30 autistic children without obesity in Group II (age: 5.71 ± 1.5; 22 males and eight females). They visited the clinics in the Medical Research Centre of Excellence, National Research Centre, Cairo, Egypt. They were diagnosed to have ASD according to the criteria of DSM-5 [21] and by autism diagnostic interview-revised [22]. Inclusion criteria for participants were having an ASD with a body mass index (BMI) more than 95th percentile for children in Group I and having BMI <85th percentile for cases in Group II and having a chronological age range of 3–10 years for both groups. Exclusion criteria were having abnormal general or neurological examination, abnormal motor development, and abnormal facial features suggestive of syndromic involvement, having sleep disorder or MRI abnormalities and being on antipsychotic therapy. The participants were subjected to interviewing for medical history, general examination, otorhinolaryngological examination, and neurological examination. The childhood autism rating scale (CARS) was used for the severity of ASD to be determined [23]. Evaluation to judge the intellectual functioning of the participants was performed by the Arabic version of Stanford Binet Intelligence Scales: Fifth Edition [24], [25]. The Arabic Preschool Language Scale was used for obtaining the language age using the raw scores of the receptive and expressive language abilities in the scale. The scaled scores for receptive and expressive language together with total language performance were used to verify the presence of developmental language delay [26]. Furthermore, 1 h electroencephalogram (EEG) was performed. Blood samples were obtained from all participants. Serum BDNF concentration was estimated by sandwich ELISA method using the Human BDNF ELISA kit (Sunlong Biotech Co.) [27]. Determination of serotonin serum level was carried out using high-performance liquid chromatography system, Agilent technologies 1100 series, and equipped with a quaternary pump (Quat pump, G131A model) [28]. Written informed consents were obtained from the parents of participants. The study was approved by the Medical research ethics committee of the National Research Centre. Data were analyzed by SPSS computer package with the version 19 windows. When $p < 0.05$, the null hypothesis was rejected and results were found to be significant.

Results

The severity of ASD for participants ranged from mild-moderate to severe degree. CARS scores range

in Group I was (30–38.5) while in Group II was (30–36.5). Children in both groups had intellectual delay or disability. All participants manifested delayed language development as detected by the language scale. There was no significant statistical difference between the groups regarding the CARS scores, IQ level, or language age (Table 1). However, children in Group I had less IQ scores and less language age than those in Group II (IQ range in Groups I and II: 40–68 and 41–72, respectively). The language age for the participants in Group I was less than that in Group II (language age range in Groups I and II: 0.6–3.3 and 1–4.1, respectively). None of the participants had EEG changes. The level of BDNF in Group I was less than that in Group II. The level of serotonin in Group I was more than that in Group II. The levels of both markers showed statistically significant difference between groups (Table 1).

Table 1: The difference between autistic cases with obesity and autistic cases without obesity regarding the CARS scores, IQ, language age, BDNF, and serotonin serum levels

Item	Group I (with obesity)	Group II (without obesity)	p value
CARS score	34.03 ± 4.3	34.08 ± 2.1	0.9
IQ	52.5 ± 7.2	55.5 ± 7.9	0.3
Language age (years)	1.6 ± 0.9	1.8 ± 0.7	0.1
BDNF (pg/ml)	116.04 ± 32.1	152.89 ± 65.3	0.04*
Serotonin (μg/ml)	82.9 ± 39.2	22.6 ± 4.2	<0.0001*

CARS: Childhood autism rating scale, IQ: Intelligence quotient, BDNF: Brain derived neurotrophic factor. *The value is significant at the $P \leq 0.05$ level.

Discussion

The dysregulation of BDNF and 5-HT signaling has been implicated in the ASD pathogenesis [29], [30]. Furthermore, these neurotransmitters have been involved in metabolic disorders such as obesity. Energy homeostasis is established by food intake which is controlled by hormonal signaling and multiple molecules such as BDNF and 5-HT [31], [32]. In addition to homeostasis, BDNF has a role in memory, learning, and emotional control which are essential for intellectual functioning, behavior, and language development. Therefore, estimating BDNF and 5-HT levels in autistic children with obesity compared to autistic children without obesity could highlight their role in obesity manifested by ASD children. Furthermore, investigating the influence of obesity on severity of ASD, intellectual, and language development is also essential. This would give suggestions about proper obesity management for such children in the future.

BDNF has various roles including neurotrophic activity, inflammation control, and metabolism. It has been hypothesized to be responsible for the tight interaction between brain, the immune system, and the adipose tissue [33]. BDNF is highly expressed in hypothalamus which is responsible for motivation, emotional response, and hormonal balance. Hypothalamus was found to be reduced in volume in ASD individuals. Elevated BDNF in ASD individuals could be a compensation for such reduction [4]. The level of BDNF was found to be significantly reduced in obese autistic children when compared to non-obese autistic children in this study. The IQ and language age of the obese participants were less than those of non-obese ones which could be related to the lower BDNF levels. Episodic memory which is involved in intellectual functioning and language development was reported to depend on brain BDNF [34]. Furthermore, obese children were reported to have altered leptin functioning. Leptin is involved in activation of neurons in hippocampus and limbic system which are related to language and memory development [35]. BDNF acts as a key which regulates weight and food intake. It produces the fullness feeling. Furthermore, it improves cellular insulin sensitivity. It has been proposed as an anti-hyperlipidemic and anti-diabetic treatment [32]. Therefore, its reduction in Group I participants could be involved in their obesity.

It has been reported that low brain serotonin was involved in obesity. Serotonin has a role in controlling satiety and body fat distribution. Moreover, there is a mutual inhibition between 5-HT and dopaminergic systems. The decrease in dopamine mediated reward mechanism leads to increased food intake. On the other hand, high peripheral 5-HT which is mostly derived from gut was found to induce obesity in non-autistic individuals. More cells that are responsible for producing serotonin were detected in the intestine of obese individuals. The gut-derived 5-HT was suggested to be an important driver of human obesity as well as of dysglycemia [31]. Further, high peripheral 5-HT was shown to suppress the adaptive thermogenesis in brown adipose tissue which causes obesity [36]. It is noteworthy that metabolic diseases such as obesity and diabetes (type 2) were associated with decreased thermogenic capacity in brown and beige adipose tissues which could be related to serotonin. Furthermore, peripheral serotonin may have a role in obesity through interaction with leptin.

Leptin is a hormone secreted by adipose tissue which inhibits appetite and regulates body fat and energy. Leptin could also be related to the metabolic role of BDNF. Leptin controls satiety by acting on hypothalamus which is an area where BDNF is highly expressed [37]. High level of leptin excretion due to obesity leads to more fat accrual, hyperglycemia, hyperinsulinemia, and decrease in energy expenditure which all lead to more obesity [38]. Leptin was reported to influence the functioning of hippocampus which suggests its involvement in behavior and memory [39]. BDNF and 5-HT interfere together with other factors to influence the metabolic control of autistic children. The disturbance and changes in their levels may have a potential role in cognitive and language development of autistic children considering their role on brain development which was reported by the previous studies such as Duff and Brown-Schmidt [34] and Meneses and Liy-Salmeron [40]. The influence of obesity on ASD severity, intellectual, and language

development of ASD children was not distinctive in this study. Nevertheless, further wide scale investigations are needed to verify this issue considering the detected statistically significant changes in the levels of targeted markers in obese autistic children in this study.

Conclusion

The difference between obese and non-obese autistic children in the levels of BDNF and serotonin could be related to obesity in the participants of this study. The influence of obesity on ASD severity, intellectual, and language development of ASD children was not distinctive in the participants. The influence of such markers on ASD severity and cognitive performance needs further investigations.

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Compliance with Ethical Standards

Availability of data and material

All data are original and available from the corresponding author on reasonable request.

Ethics approval

"The study was approved by the Medical Research Ethics Committee of the National Research Centre, Egypt."

Consent to participate

Signed informed consents were taken from the parents of the children after explaining the aim and procedures of the study.

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