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Relation of insulin resistance to neurocognitive function and electroencephalography in obese children

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Abstract

Background: Childhood obesity may lead to neuronal impairment in both the peripheral and the central nervous system. This study aimed to investigate the impact of obesity and insulin resistance (IR) on the central nervous system and neurocognitive functions in children.
Methods: Seventy-three obese children (38 male and 35 female) and 42 healthy children (21 male and 21 female) were recruited. Standard biochemical indices and IR were evaluated. The Wechsler Intelligence Scale for Children-Revised (WISC-R) and electroencephalography (EEG) were administered to all participants. The obese participants were divided into two groups based on the presence or absence of IR, and the data were compared between the subgroups.
Results: Only verbal scores on the WISC-R in the IR+ group were significantly lower than those of the control and IR– groups. There were no differences between the groups with respect to other parameters of the WISC-R or the EEG. Verbal scores of the WISC-R were negatively correlated with obesity duration and homeostatic model assessment-insulin resistance (HOMA-IR) values. EEGs showed significantly more frequent 'slowing during hyperventilation' (SDHs) in obese children than non-obese children.
Conclusions: Neurocognitive functions, particularly verbal abilities, were impaired in obese children with IR. An early examination of cognitive functions may help identify and correct such abnormalities in obese children.

Keywords: electroencephalography; insulin resistance; neurocognitive function; obesity.

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Introduction

The increasing prevalence of childhood obesity has led to a greater incidence of associated morbidities such as neuronal dysfunction [1, 2], as obesity is associated with both peripheral neuropathy and central nervous system dysfunction, including neurocognitive impairment [3].

Insulin resistance (IR) is an important consequence of obesity and has been thought to be significant in the pathogenesis of neuronal impairment [4]. Additionally, insulin is critical for neuronal development, migration, myelin, and neurotransmitter production, the formation of synapses, neuronal plasticity and gene expression [5–8].

Electrophysiological studies have revealed an association between impaired peripheral nerve conduction and IR in obese children [9, 10], and inspired other studies showing that visual and auditory pathways are also affected by hyperinsulinemia [11]. Electroencephalography (EEG) is a valuable tool for demonstrating abnormalities in the central nervous system [12].

Thus, the purpose of this study was to evaluate the relationship among EEG findings, Wechsler Intelligence Scale for Children Revised (WISC-R) parameters, obesity and IR to investigate the impact of obesity and IR on central nervous system function and neurocognition.

Materials and methods

Participants were 73 children with obesity (35 male and 38 female) admitted to the pediatric endocrinology outpatient department and 42 non-obese children (21 male and 21 female), as controls, admitted to the pediatric outpatient department for various symptoms unrelated to obesity or its complications. Obesity was defined as a body

mass index (BMI) above the 95th percentile [13]. The data on obesity duration were obtained from the parents and medical records of the patients. The children enrolled in the control group had a BMI between the 10th and 85th percentiles. All anthropometric measurements were obtained by the same group of trained staff. Weight was measured using a digital weighing scale (SECA 841, Hamburg, Germany, accuracy of 100 g) with the children wearing only underwear. Height was measured using a stadiometer (accuracy 0.1 cm) without shoes. BMI was calculated as weight divided by height squared (kg/m^2) and then converted to a sex- and age-specific BMI standard deviation score (SDS) and percentile value. The pubertal status of children was determined according to the Tanner stages. Prepubertal children and participants with any neurological, psychiatric, or systemic disorders were excluded. The children with obstructive sleep apnea (OSA) symptoms such as snoring and restless sleep were also not included in the study.

Fasting glucose, high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglyceride (TG) levels were enzymatically determined by blood samples on an autoanalyzer (Olympus 2700, Olympus Medical Systems, Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula. Plasma insulin levels were assayed by the ELISA on an automated immunoassay analyzer (E170; Roche Diagnostics, Holliston, USA). IR was calculated according to the homeostasis model of assessment (HOMA) formula: fasting insulin (IU/mL) × fasting glucose (mg/dL)/405. A HOMA value >4 was considered as IR [14, 15].

Electroencephalograms were recorded on a 32-channel digital electroencephalograph (Galileo NT, EBNeuro, Firenze, Italy). Recordings were performed with silver/silver chloride electrodes, applied to the scalp with collodion, according to the International 10–20 System [16]. Ear electrodes served as a reference for all electrodes and the ground electrode was attached to the forehead. The recording parameters used were sensitivity 10 μV/mm, low-pass filters set at 50 Hz, high-pass filters, and a set-up time constant of 0.1 s. During the EEG recording, the short periods of photic stimulation and hyperventilation (HV) were also included. All participants hyperventilated continuously with eyes closed in the supine position for 3 min. The EEG technologist demonstrated to all participants the rate and depth of HV effort before the recording.

The WISC-R test is an individually administered intelligence test validated for children aged between 6 and 16 years. The test includes six verbal (general similarities, information, judgment, vocabulary, arithmetic and digit span) and six performance (picture completion, object assembly, block design, picture arrangement, labyrinths and digit symbol) subscales. The validity and reliability of the WISC-R for Turkish children and adolescents has been previously confirmed [17, 18]. The scale was administered in the morning after a good sleep and when the children were not hungry. Verbal performance and total IQ scores were also acquired and included in the analysis.

For descriptive data, percentage and number for categorical variables and mean ± standard deviation values for continuous variables were used. Group comparisons were made using the chi-square (χ^2) test for categorical variables and Student's t-test for continuous variables. One-way analysis of variance (ANOVA) was used for comparing continuous variables among the three groups, and Tukey's post-hoc test was used for establishing significance. The correlation between variables was evaluated by Pearson's test. SPSS Statistics package (Ver. 21.0 IBM, Chicago, IL, USA) was used for all calculations and a p-value of 0.05 was used to define statistically significant differences.

An informed consent form was obtained from parents and the study was approved by the Institutional Review Board.

Results

No differences were found between the obese and non-obese children with respect to age and sex. In obese children, blood glucose, TG, TC, HOMA-IR, LDL-C, plasma insulin and BMI-SDS values were significantly higher whereas HDL-C levels were significantly lower, compared to the control group (Table 1).

Obese children were further grouped as either having (IR+, n = 31) or not (IR–, n = 42). Fasting plasma insulin and glucose levels were significantly higher in the IR+ group but there were no statistically significant differences between the IR– and IR+ groups in other metabolic and anthropometric variables (Table 2).

EEG and WISC-R findings in IR+ obese children, IR– obese children, and non-obese children were compared (Table 3). Verbal scores for the WISC-R scale were significantly lower in the IR+ group compared to the control or IR– groups. There were no differences among the three groups with respect to other parameters of the WISC-R scale or the EEG.

The correlation analysis between WISC-R scores and age, obesity duration, HOMA-IR, fasting plasma insulin, BMI-SDS, or fasting blood glucose levels was performed (Table 4), which showed that verbal and total scores of the WISC-R were negatively correlated with HOMA-IR values.

Table 1: Clinical and laboratory findings of the study groups.

	Obese group n = 73	Control group n = 42	p-Value
Age, year	11.8 ± 2.5	11.5 ± 2.3	0.24
Gender (F/M)	35/38	21/21	0.21
BMI-SDS	2.0 ± 0.4	0.26 ± 0.4	<0.001
Fasting blood glucose, mg/dL	92.1 ± 8.3	88.0 ± 11.2	<0.001
Fasting plasma insulin, μIU/mL	17.4 ± 5.6	6.7 ± 2.9	<0.001
HOMA-IR	4.1 ± 1.8	1.5 ± 0.6	<0.001
TG, mg/dL	144.1 ± 52.9	91.0 ± 47.5	<0.001
TC, mg/dL	178.3 ± 29.7	156.6 ± 28.0	<0.001
HDL-C, mg/dL	45.7 ± 8.8	52.8 ± 10.5	0.003
LDL-C, mg/dL	104.3 ± 32.3	82.1 ± 24.3	0.001

BMI-SDS, body mass index standard deviation score; HOMA-IR, homeostasis model of assessment-insulin resistance; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-denstiy lipoprotein cholesterol. Data are presented as mean ± SD.

Table 2: Clinical and laboratory findings of the study groups according to insulin resistance.

	Obese		Control group n=42	p-Value
	IR+ group n=31	IR− group n=42		
Age, year	12.4±2.3	11.4±2.4	11.5±2.3	0.15
Gender (F/M)	17/14	18/24	21/21	0.58
Obesity duration, year	4.9±2.6	4.7±2.4		0.59
BMI-SDS	2.1±0.37	2.0±0.29	0.26±0.4	<0.001[a,b]
Fasting blood glucose, mg/dL	96.3±9.1	88.5±7.3	88.0±11.2	0.001[a,c]
Fasting plasma insulin, µIU/mL	24.6±9.0	11.7±3.6	6.7±2.9	<0.001[a,c]
HOMA-IR	6.1±2.0	2.6±0.8	1.5±0.6	<0.001[a,c]
TG, mg/dL	145.0±65.6	144.1±45.9	91.0±47.5	<0.001[a,b]
TC, mg/dL	173.0±28.4	183.4±32.7	156.6±28.0	<0.001[a,b]
HDL-C, mg/dL	44.5±8.9	46.7±8.9	52.8±10.5	0.003[a,b]
LDL-C, mg/dL	98.2±26.8	108.2±32.0	82.1±24.3	0.002[a,b]

BMI-SDS, body mass index standard deviation score; HOMA-IR, homeostasis model of assessment-insulin resistance; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-denstiy lipoprotein cholesterol. Data are presented as mean ± SD. [a]Statistically significant difference between IR+ group and control group. [b]Statistically significant difference between IR− group and control group. [c]Statistically significant difference between IR+ group and IR− group.

Table 3: WISC-R and EEG parameters of the study groups according to insulin resistance.

	Obese		Control group n=42	p-Value
	IR+ group n=31	IR− group n=42		
WISC-R				
Verbal	94.3±12.4	101.1±11.3	103.2±15.6	0.02[a,b]
Performance	101.0±14.2	100.8±12.8	100.2±12.9	0.96
Total	97.2±13.9	100.9±11.8	102.0±11.4	0.11
EEG				
Frequency, Hz	9.9±0.7	9.9±0.8	9.9±0.5	0.87
Abnormality, %	0	2.4	2.4	0.41
Slowing during hyperventilation, %	35.5	31.0	14.3	0.08
Response to photic stimulation, %	0	0	2.4	0.42

WISC-R, Wechsler Intelligence Scale for Children-Revised; EEG, electroencephalography. [a]Statistically significant difference between IR+ group and control group. [b]Statistically significant difference between IR+ group and IR− group.

Table 4: Correlation analysis of WISC-R parameters and HOMA-IR, BMI, fasting blood glucose, fasting plasma insulin, age and obesity duration in the obese group.

	HOMA-IR	BMI-SDS	Fasting blood glucose	Fasting plasma insulin	Age	Obesity duration
Verbal						
r	**−0.325**	−0.147	−0.136	**−0.295**	−0.316	**−0.336**
p-Value	**0.03**	0.12	0.16	**0.05**	0.09	**0.04**
Performance						
r	−0.063	−0.038	0.010	−0.057	−0.036	−0.096
p-Value	0.52	0.69	0.91	0.56	0.32	0.10
Total						
r	**−0.242**	−0.098	−0.099	−0.172	−0.214	−0.136
p-Value	**0.05**	0.30	0.31	0.08	0.10	0.16

HOMA-IR, homeostasis model of assessment-insulin resistance; BMI-SDS, body mass index standard deviation score; WISC-R, Wechsler Intelligence Scale for Children-Revised. Values in bold indicate the significant correlations.

Table 5: WISC-R and EEG parameters of the study groups according to obesity.

	Obese n=73	Control group n=42	p-Value
WISC-R			
Verbal	98.2±12.2	103.2±15.6	0.06
Performance	100.9.2±13.4	100.2±12.9	0.80
Total	98.6±12.9	102.0±11.4	0.17
EEG			
Frequency, Hz	9.9±0.7	9.9±0.5	0.64
Abnormality, %	0	2.4	0.19
Slowing during hyperventilation, %	32.9	14.3	**0.03**
Response to photic stimulation, %	0	2.4	0.19

WISC-R, Wechsler Intelligence Scale for Children-Revised; EEG, electroencephalography. Value in bold indicates the significant difference between obese and control groups.

Verbal scores were also negatively correlated with obesity duration and fasting plasma insulin levels.

In the EEG study, slowing during hyperventilation (SDH) was seen significantly more frequently in obese children than non-obese children, while response to photic stimulation and alpha frequency index were similar between obese children and controls (Table 5).

Discussion

In this study, we found that verbal intelligence scores were lower in obese children with IR compared to those without IR or controls. Further, verbal and total scores in the WISC-R and HOMA-IR levels were negatively correlated. Verbal WISC-R scores were also negatively correlated with the duration of obesity.

The essentiality of insulin in regulating energy homeostasis in the central nervous system has been shown in animal studies [19, 20], and it is known that insulin receptors are present in the hippocampus and in cortical brain structures [21]. On the other hand, it has been shown in obese patients that the central nervous system displays reduced sensitivity to the effects of insulin. Specifically, magnetoencephalography studies have demonstrated decreased cortical activity upon insulin infusion in overweight and obese patients compared to normal weight participants [22]. Further, the increased plasma insulin concentrations were found to be correlated with cerebrospinal fluid (CSF) insulin levels [23]; however, this correlation was not found to be valid in the obese patients and as plasma insulin levels increased, the ratio of CSF to plasma insulin levels decreased [24]. The studies done on animals have revealed that obesity leads to a reduction in insulin binding onto receptors on the endothelial cells of brain microvessels and impairs transendothelial transport across the brain-blood barrier [25]. Human and animal studies also indicate that obesity and IR are related to cognitive dysfunction [26–28]. In our study, we investigated cognitive functions using the WISC-R scale. Similarly, another study that used the WISC-R also showed cognitive impairment in obese children compared to non-obese participants [29] and related this finding to the presence of OSA. However, we observed an association between cognitive impairment and IR even though children with OSA symptoms were excluded from the study. Previous reports have revealed that IR-related disorders, such as the metabolic syndrome and type-2 diabetes, are also associated with neurocognitive dysfunction [30, 31] and it has been suggested that the effects of IR on CNS function are probably due to the abnormalities in vascular reactivity to insulin [32]. Specifically, if a defined region of the brain is activated during cognitive functioning, this activation causes local vasodilatation to clear metabolic products [33]; however, an endothelial damage due to IR can impair such regional vasodilatation [34].

We found that IR particularly impaired verbal intelligence in obese patients. Previous studies have also revealed that obesity-dependent deficits in cognition predominantly involved executive functions [35, 36]. It has been shown that insulin increases memory, probably by binding to receptors in the hippocampus and the limbic part of the brain [37], while other studies show that insulin administration improves memory functions in non-obese patients [38, 39]. However, in obese patients, insulin sensitivity is reduced and the resulting impairment in vocabulary memory can lead to verbal disabilities. Moreover, the main brain region related to verbal cognitive functions is the frontal lobe and it develops during adolescence period. Therefore, metabolic disturbances such as IR, occurring during this period, can primarily affect this region [40].

We also found a negative correlation between verbal intelligence and obesity duration, indicating that verbal function impairment may be a complication of obesity that is related to the presence of IR. However, we could not obtain data on the duration of IR in our patients. Further, due to the cross-sectional design of the study, no comparisons could be made between verbal acuity before and after the onset of obesity. Therefore, we speculate that lower WISC-R scores may be caused by obesity. Other reports also show that a majority of people with intellectual

disabilities tend to perform low physical activity [41], and that similarly, awareness, and motivation for maintaining a proper diet and healthy life style are probably more difficult for people with cognitive disabilities [42].

Insulin administration was found to have rapid effects on EEG waveforms. A sleep-EEG study showed an association between slow wave activities and IR in obese adolescents; however, we found no association between hyperinsulinemia and EEG results [43, 44]. Various electrophysiological impairments in obese children attributable to IR have been reported. Nerve conduction studies have indicated abnormalities in obese children with IR compared to both obese and non-obese children without IR [9]. Brain auditory evoked potentials (BAEP) were found to be lower, particularly in the peripheral auditory nervous system in obese children with IR [11], suggesting that impairment of electrophysiological parameters due to hyperinsulinemia begins from the peripheral parts of the nervous system.

When we compared the control group with all obese participants, we found that SDH was seen significantly more frequently in obese children compared to non-obese children. There were no other differences between the groups in the EEG findings, although eating disorders have been reported to be associated with EEG abnormalities in obese patients [45, 46]. Furthermore, one study indicated that obese participants without eating disorders showed poor alpha desynchronization [47]. Another study suggested that obesity in patients was associated with abnormal cortical neural synchronization at the base of alpha rhythms. However, we saw no such differences in alpha rhythms between the obese and non-obese subjects, and SDH was the only significantly different finding between the groups. As SDH also occurs in normal children due to a decrease in cerebral blood flow, it is thought that the response to a change in pCO_2 leads to a decrease in cerebral blood flow [43, 48]. Thus, more frequent SDH in obese patients could be the result of brain vascular reactivity dysregulation due to IR or inflammation.

The present study has a cross-sectional design; consequently, our data represent a one-time "snapshot" of the neurocognitive status and EEG profile of the subjects. Therefore, future studies should have a prospective, longitudinal design to reveal a "cause and effect relationship", if any, between IR and verbal intelligence. In our study, IR was measured by calculating HOMA-IR instead of the glucose clamp technique, which is the gold standard method. Moreover, the controlled design of the study and classification based on IR could help elucidate the physiologic mechanisms associated with neurocognitive pathologies.

In conclusion, we demonstrate neurocognitive abnormalities in obese children with IR compared to obese or non-obese subjects without IR. Early examination of cognitive functions by the WISC-R may help detect and address such deficiencies in obese children.

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