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Research report

Association between obesity-related biomarkers and cognitive and motor development in infants

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ABSTRACT

Background: This study aimed to verify the association between obesity-related biomarkers and cognitive and motor development in infants between 6 and 24 months of age.

Methods: A cross-sectional study was conducted with 50 infants and plasma levels of leptin, adiponectin, resistin, soluble tumor necrosis factor receptors 1 and 2 (sTNFR1 and sTNFR2), chemokines, brain-derived neurotrophic factor (BDNF), serum cortisol and redox status were measured. The Bayley-III test was utilized to evaluate cognitive and motor development, and multiple linear stepwise regression models were performed to verify the association between selected biomarkers and cognitive and motor development.

Results: A significant association was found among plasma leptin and sTNFR1 levels with cognitive composite scores, and these two independent variables together explained 37% of the variability of cognitive composite scores ($p = 0.001$). Only plasma sTNFR1 levels were associated and explained 24% of the variability of motor composite scores ($p = 0.003$).

Conclusions: Plasma levels of sTNFR1 were associated with the increase in cognitive and motor development scores in infants between 6 and 24 months of age through a mechanism not directly related to excess body weight. Moreover, increase in plasma levels of leptin reduced the cognitive development in this age range.

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1. Introduction

The first 24 months of age represent an important period for the development of overweight and obesity in childhood and its long-term health consequences [1]. In this period, the brain develops rapidly [2] and early unfavorable conditions that affect the health and growth of infants can impair the normal development of the brain. Therefore, the exposure to potential effects of obesity-related biomarkers may affect the organization of the developing brain [3] during this critical period for infant cognitive and motor development [4].

Adipose tissue produces substances called adipokines that communicate with multiple tissue and organ systems, including the brain, to regulate metabolism [5]. Some adipokines like leptin have central actions in the hypothalamus and the hippocampus that go beyond regulation of energy homeostasis and influence brain growth, maturation and development [6,7]. Other adipokines released from adipose tissue in obese individuals detect metabolic stress and modulate metabolic adaptation by regulating immune function in chronic obesity [5,8]. Higher levels of systemic pro-inflammatory biomarkers such as tumor necrosis factor (TNF) may cross the blood-brain barrier and the central nervous system; thus, the central nervous system can be affected by actions of inflammatory mediators originating from the periphery [5,9] and may potentially impair critical learning skills [5]. In addition to adipokines, redox imbalance, cortisol hormone and neurotrophic factors may also affect brain structure and functions and are relevant to neurodevelopment [10–13].

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Table 1
Mean, SD and range of the biomarkers levels and composite scores.

Variables	Mean (SD)	Minimum–Maximum
Leptin (pg/mL)	1750.26 (±763.28)	344.85–3118.69
Adiponectin (pg/mL)	44220.46 (±4398.87)	31368.10–52001.23
Resistin (pg/mL)	2762.82 (±490.96)	1665.08–3760.51
sTNFR1 (pg/mL)	1354.51 (±509.65)	656.64–3808.24
sTNFR2 (pg/mL)	3440.75 (±1045.65)	1792.20–7644.50
MCP-1 (pg/mL)	211.18 (±130.04)	60.82–585.82
IL-8 (pg/mL)	5.17 (±4.95)	0.00–33.56
RANTES (pg/mL)	2818.75 (±1718.79)	375.57–9845.25
IP-10 (pg/mL)	96.24 (±122.66)	16.90 – 821.53
MIG (pg/mL)	75.39 (±132.46)	6.85–786.91
BDNF (pg/mL)	5408.51 (±3552.49)	1607.57–15136.40
Cortisol (nmol/L)	2.78 (±1.29)	82.49–603.39
TBARS (nmolMDA/mg protein)	16.30 (±1.38)	4.07–68.60
SOD (U/mg protein)	9.42 (±7.84)	2.16–38.44
CAT (ΔE/min/mg)	1.03 (±6.92)	33.36–307.52
FRAP (μg FeSO ₄ /mg protein)	2.20 (±2.88)	37.50–1426.30
Cognitive composite scores	103.60 (±9.37)	80.00–120.00
Motor composite scores	100.02 (±10.59)	79.00–124.00

Legend: sTNFR1, soluble tumor necrosis factor receptor 1; sTNFR2, soluble tumor necrosis factor receptor 2; MCP-1, monocyte chemoattractant protein-1; IL8, interleukin 8; RANTES, regulated upon activation of normal expressed and secreted T-cells; IP-10, interferon-inducible protein 10; MIG, monokine induced by interferon-γ; BDNF, brain-derived neurotrophic factor; TBARS, thiobarbituric acid reactive substances; SOD, superoxide dismutase; CAT, catalase, FRAP, ferric reducing antioxidant power.

Overweight and obesity in childhood are associated with a cascade of neuroendocrine inflammatory changes that activate a chronic low-grade inflammation state and redox imbalance. Studies have shown that higher levels of leptin, resistin, TNF, sTNFR1 and sTNFR2, chemokines, thiobarbituric acid reactive substances (TBARS) and cortisol, as well as lower levels of adiponectin, BDNF and the antioxidant superoxide dismutase (SOD) and catalase (CAT) enzymes exist in school-age overweight or obese children [14–17]. A recent study of our group showed that higher levels of leptin, adiponectin, BDNF and cortisol, as well as lower levels of TBARS and lower SOD and CAT activity are present in overweight/obese infants than in their normal-weight peers between the ages of 6 and 24 months of age [18].

Other prior study of our group has pointed out that overweight and obese infants demonstrates lower cognitive and motor development scores than normal-weight peers [19]. However, few studies have considered possible biomarkers linking obesity and developmental outcomes [5,11] and significant gaps remain to be understood. Considering that other studies have demonstrated that overweight and obesity in childhood present an inverse relationship with cognitive and motor development [20,21], we hypothesized that obesity-related biomarkers would be associated with cognitive and motor development in infancy. The aim of this study was to verify the association of the plasmatic levels of adipokines [leptin, adiponectin, resistin, sTNFR1 and sTNFR2, monocyte chemoattractant protein-1 (MCP-1), regulated upon activation normal T-cell expressed and secreted (RANTES), interleukin-8 (IL-8), interferon-inducible protein 10 (IP-10), monokine induced by interferon-γ (MIG)], BDNF, serum cortisol, TBARS levels, SOD and CAT activity and ferric reducing antioxidant power (FRAP) with cognitive and motor development in obese, overweight and normal-weight infants between 6 and 24 months of age. Potential contributing factors for developmental delay will help to implement intervention strategies.

2. Methods

Fifty infants were evaluated (25 in the overweight/obese group and 25 in the normal-weight group). The Table 1 shows the mean,

Table 2
Simple linear regression analysis with cognitive composite and motor composite scores.

Biomarkers	Cognitive composite scores		Motor composite scores	
	β	p	β	p
Leptin	-0.30	0.04*	–	–
sTNFR1	0.49	0.0001*	0.41	0.003*
sTNFR2	0.35	0.01*	0.38	0.006*
IL8	0.18	0.21	–	–
RANTES	–	–	-0.17	0.25
SOD	–	–	0.31	0.08
CAT	–	–	0.39	0.03*
FRAP	–	–	0.30	0.11

Legend: β, standardized regression coefficient; sTNFR1, soluble tumor necrosis factor receptor 1; sTNFR2, soluble tumor necrosis factor receptor 2; IL8, interleukin 8; RANTES, regulated upon activation of normal expressed and secreted T-cells; SOD, superoxide dismutase; CAT, catalase, FRAP, ferric reducing antioxidant power.

Table 3
Multiple linear stepwise regression analysis.

Biomarkers	Cognitive composite scores			Motor composite scores		
	β	p	R ²	β	p	R ²
			0.37			0.24
Leptin (pg/mL)	-0.40	0.001*				
sTNFR1 (pg/mL)	0.56	0.0001*		0.51	0.003*	
sTNFR2 (pg/mL)	-0.14	0.40		0.11	0.66	
CAT (ΔE/min/mg)				0.22	0.16	

Legend: β, standardized regression coefficient; R², adjusted determination coefficient; sTNFR1, soluble tumor necrosis factor receptor 1; sTNFR2, soluble tumor necrosis factor receptor 2; CAT, catalase.

standard deviation (SD) and range of the biomarkers levels, as well cognitive and motor composite scores.

Among the sixteen biomarkers evaluated in plasma, serum or erythrocyte lysate, four biomarkers correlated with cognitive composite scores ($p > 0.20$): leptin (Spearman $r = -0.29$; $p = 0.04$); sTNFR1 (Spearman $r = 0.52$; $p = 0.0001$); sTNFR2 (Spearman $r = 0.26$; $p = 0.07$) and IL8 (Spearman $r = 0.23$; $p = 0.11$). With regard to the motor composite scores, six biomarkers presented a p value lower than 0.20: sTNFR1 (Pearson $r = 0.39$; $p = 0.005$); sTNFR2 (Pearson $r = 0.35$; $p = 0.01$); RANTES (Pearson $r = -0.22$; $p = 0.13$); SOD (Pearson $r = 0.31$; $p = 0.08$), CAT (Pearson $r = 0.39$; $p = 0.03$) and FRAP (Pearson $r = 0.30$; $p = 0.12$). These biomarkers were selected for simple linear regression analysis.

Only leptin, sTNFR1 and sTNFR2 biomarkers were significantly associated with cognitive composite scores ($p < 0.05$), and sTNFR1, sTNFR2 and CAT biomarkers were significantly associated with motor composite scores ($p < 0.05$) (Table 2). Multiple linear stepwise regression models were tested (Table 3).

From the multiple linear regression analysis, a significant association of plasma leptin and sTNFR1 levels with cognitive composite scores was observed, and these two independent variables together explained 37% of the variability of cognitive composite scores ($p = 0.001$). However, only plasma sTNFR1 levels were associated with and explained 24% of the variability of motor composite scores ($p = 0.003$). In this way, plasma sTNFR1 levels were positively associated because the increase of 1 pg/mL in sTNFR1 level lead to an increase of 0.56 points in cognitive composite score and 0.51 points in motor composite score (Table 3). Already elevated plasma leptin levels were significantly negatively associated because an increase of 1 pg/mL in leptin level lead to a decrease of 0.40 points in cognitive composite scores. After adjusting for age and gender, there were no differences in the β and R² values, thereby demonstrating that these factors were not found to affect measurement confounders in our sample.

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