Avni Kaya*, Zerrin Orbak, İsmail Polat, Harun Polat and Musa Gümüşdere

Leptin and neuropeptide Y levels in newborns

DOI 10.1515/jpem-2015-0201
Received May 14, 2015; accepted August 3, 2015; previously published online September 3, 2015

Abstract

Aim: Several studies have investigated leptin and neuropeptide Y (NPY) levels in children, but the information for newborns in the literature is limited. The purpose of this study was to determine leptin and NPY levels in 14- to 28-day-old newborns.

Materials and methods: This prospective study was performed in Atatürk University Medical Faculty Research Hospital Neonatal Clinic, Erzurum, Turkey between July and December, 2014. Sixty-two 14- to 28-day-old neonates, 26 female and 36 male, were included. Age, height, and body weight of the patients were recorded. Feeding status was also recorded. The newborns were divided into two groups – those receiving breastfeeding only and those receiving breastfeeding and formula. Plasma leptin levels were measured using enzyme amplified sensitivity immunoassay (EASIA).

Results: The mean leptin level in 14- to 28-day-old female neonates was 4.25±3.08 ng/mL, and the mean NPY level was 24.79±9.87 ng/mL. The mean leptin level in 14- to 28-day male neonates was 3.49±2.52 ng/mL, and the mean NPY level was 25.80±9.58 ng/mL. No significant difference was determined between leptin (p=0.228) or NPY (p=0.144) in terms of feeding status. No significant difference was also observed between the sex in terms of leptin or NPY levels (leptin p=0.775 and NPY p=0.687).

Conclusion: There were no differences in terms of feeding status and sex in leptin and NPY levels in the neonatal period.

Keywords: leptin; neuropeptide Y; newborn.

***Corresponding author: Avni Kaya,** Faculty of Medicine, Department of Pediatric Endocrinology, Ataturk University, Erzurum, Turkey, Phone: +904422317824, Fax: +4422361301, Cell: +905052677045, E-mail: avnikaya@gmail.com
Zerrin Orbak and İsmail Polat: Faculty of Medicine, Department of Pediatric Endocrinology, Ataturk University, Erzurum, Turkey
Harun Polat and Musa Gümüşdere: Faculty of Medicine, Department of Biochemistry, Ataturk University, Erzurum, Turkey

What's known on this subject?
Several studies have investigated leptin and neuropeptide Y levels in children, but the information for newborns in the literature is limited.

What this study adds?
This is the first study to investigate leptin and neuropeptide Y levels in healthy newborns. We describes that leptin and neuropeptide Y values of 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentiles.

Introduction

Leptin is a hormone produced from fatty tissue that controls food intake through leptin receptors in the hypothalamic arcuate nucleus. In the regulation between energy intake and consumption, neuropeptide Y (NPY) increases appetite, whereas leptin reduces it by suppressing NPY secretion. Leptin concentrations are related to fatty tissue; leptin levels decrease in lipodystrophic conditions, anorexia, and hunger, and increase in satiation and weight gain (1–3). It has been suggested that leptin triggers precocious activation of hypothalamic-pituitary-gonadal axis in puberty. It has also been shown to trigger onset of puberty in boys (4). It is a metabolic signal protein that informs the hypothalamus that sufficient energy for pubertal development has been stored. Leptin levels gradually increase until birth and decline dramatically after birth in healthy neonates. This may be important for the stimulation of feeding behavior, fetal development, and the acquisition of energy homeostasis in the neonate (5).

Several studies have investigated leptin and NPY levels in children, but the information for newborns in the literature is limited, especially in terms of NPY (5–9). The purpose of this study was to determine leptin and NPY levels in newborns aged from 14 to 28 days.

Materials and methods

This prospective study was intended to determine plasma leptin and plasma NPY levels in neonates admitted to Atatürk University Medical Faculty Research Hospital Neonatal Clinic, Erzurum, Turkey between

July and December, 2014 after obtaining signed consent from respective families. Sixty-two newborns aged from 14 to 28 days, 26 female and 36 male, were included in the study. Newborns aged other than 14–28 days or with any disease and premature and postmature newborns were excluded. All newborns were completely healthy. Newborns aged from 14 to 28 days were selected in order to ensure standardization among patients. The hypothalamic-pituitary-gonadal axis performs standard functions at 14–28 days without the period of birth being affected. Once signed consent forms had been received, history of each newborn was taken. Patients' age, height, and body weight were recorded. Feeding status was also recorded. The newborns were divided into two groups – those receiving breastfeeding only (1st group) and those receiving breastfeeding and formula (2nd group). The newborns in the 2nd group were given both mother's milk and formula, in no specific proportions. Newborns with any disease or congenital anomaly or with mothers having chronic disease were excluded. The following laboratory protocol was applied to blood specimens collected: 2 mL of blood obtained using routine venous collection was placed into K2EDTA tubes. Specimens were centrifuged and stored at −80°C. Plasma samples were gradually thawed on the day of examination. Plasma leptin levels were measured by the enzyme amplified sensitivity immunoassay (EASIA) method using DIAsource kit (Leptin-EASIA (human) KAP2281, DIAsource ImmunoAssays S.A., Louvain-la-Neuve, Belgium). Plasma NPY levels were measured using the enzyme immunoassay (EIA) method using RayBiotech kit (NPY EIA (human) EIA-NPY-1, RayBiotech, Inc. Georgia, USA). Leptin and NPY levels were expressed as nanograms/milliliter. Ethical approval for the study was granted by the University Ethical Committee (Date 3.7.2014 Session: 7 Decision number: 5).

Statistical analysis

Patients' body weight and height were measured. Postnatal ages and body mass indices were calculated. Measurements were expressed as minimum, maximum, and mean and standard deviation. SSPE 20 for Windows software was used for data analysis. The one-sample Kolmogorov-Smirnov test was used to determine whether all numerical data for leptin and NPY in both the sex were normally distributed.

As patients' NPY values were normally distributed, the independent sample t-test was used. Leptin values were not normally distributed, and the nonparametric two independent samples Mann-Whitney U-test was therefore used. $p<0.05$ was regarded as significant at statistical analysis.

Results

Sixty-two newborns, 26 female (41.9%) and 36 male (58.1%), were included in the study. Patients' auxological characteristics and leptin and NPY levels are shown in Table 1. Fifty-two newborns (83.9%) were receiving mother's milk and 10 newborns (16.1%) mother's milk and formula. Our patients' leptin and NPY values were evaluated on the basis of 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentiles. These are shown in Table 2. No significant difference was observed between both the sex in terms of leptin or NPY levels (leptin $p=0.775$ and NPY $p=0.687$). A weak correlation was determined between leptin and NPY ($p=0.041$, $r=0.26$). No correlation was determined between leptin and body weight ($p=0.50$, $r=0.087$), length ($p=0.087$, $r=-0.21$), body mass index ($p=0.78$, $r=0.22$), age ($p=0.873$, $r=0.021$), or nutritional status ($p=0.228$, $r=-0.123$). No correlation was observed between NPY and body weight ($p=0.228$, $r=0.155$), length ($p=0.24$, $r=-0.151$), body mass index ($p=0.51$, $r=0.249$), age ($p=0.572$, $r=0.073$), or nutritional status ($p=0.144$, $r=-0.188$). These data are shown in Table 3.

Discussion

Observations show that leptin is not only involved in food intake and energy balance, but also has other metabolic and endocrinological effects (3). It has recently been discovered that leptin can modulate both synapse numbers and synaptic activity in NPY neurons in the hypothalamic arcuate nucleus (10). We detected a weak correlation between leptin and NPY in our study. While there is no doubt that leptin is involved in the onset of puberty, the existing data are insufficient to fully describe the mechanism concerned. Some authors have suggested that a high fat level is needed for the onset of puberty in rats and

Table 1: The demographic data of patients' leptin and neuropeptide Y levels minimum, maximum, mean, and standard deviation.

Parameter	Girl (n: 26)				Boy (n: 36)			
	Minimum	Maximum	Mean	Standard deviation	Minimum	Maximum	Mean	Standard deviation
Weight	3300	5300	3972.31	495.51	3500	5800	4216.67	620.36
Length	46	55	51.35	1.76	49	56	52.14	1.64
Body mass index	12.57	18.87	15.06	1.72	12.94	21.15	15.48	1.97
Age, day	14	28	20.12	4.28	15	28	21.53	3.6
Leptin	1.26	11.32	4.25	3.08	1.06	10.12	3.49	2.52
Neuropeptide Y	7.70	40.45	24.79	9.87	8.80	42.80	25.80	9.58

Table 2: Patients' plasma leptin and neuropeptide Y levels 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentile values.

Percentile	Girl (n: 26)		Boy (n: 36)		All cases (n: 62)	
	Leptin	Neuropeptide Y	Leptin	Neuropeptide Y	Leptin	Neuropeptide Y
3	1.26	7.70	1.08	8.91	1.23	8.67
10	1.34	10.64	1.48	10.98	1.47	11.15
25	1.72	19.73	1.76	21.15	1.76	19.75
50	2.31	22.87	2.45	24.85	2.44	23.62
75	7.02	34.01	4.42	34.55	6.28	34.01
90	8.73	39.85	8.13	40.12	8.18	40.03
97	11.32	40.45	10.03	42.60	10.25	41.19

Table 3: Patients' plasma leptin and neuropeptide Y levels p and r values.

Parameter	Newborns			
	Leptin		Neuropeptide Y	
	p-Value	r-Value	p-Value	r-Value
Sex	0.775			0.687
Weight, g	0.50	0.087	0.228	0.155
Length, cm	0.087	−0.21	0.24	−0.151
Body mass index, kg/m^2	0.78	0.22	0.51	0.249
Age, day	0.873	0.021	0.572	0.073
Type of nutrition	0.340	−0.123	0.144	−0.188
Leptin			0.041	0.26
Neuropeptide Y	0.041	0.26		

rodents and that a resulting rise in leptin levels may be a signal for the onset of puberty once that level of fat has been achieved (11).

Leptin levels in our study were higher in females compared to males, although the difference was not statistically significant. Mean leptin levels were 4.25 ng/mL and 3.49 ng/mL in females and males, respectively. Leptin levels being higher in females than males was attributed in one study to greater fat distribution in females (12). Another study suggested that leptin can be attributed to the pubertal increase in circulating estradiol, as clinical data suggest that estrogen increases leptin independent of body fat content in females (13).

Many studies have investigated leptin levels and NPY levels in humans. Leptin levels of –3.49±1.65 ng/mL and NPY levels of 98.5±21.9 μmol/mL have been reported in healthy children (7–17 years). That study also investigated serum leptin and NPY in children with asthma and reported no significant difference according to sex (14). Mean age of the group of children with obesity was 10.81±3.69 years. The leptin level was 36.39±43.25 ng/mL and the NPY level 1.65±2.48 ngl/mL. In the control group, the leptin level was 4.78±2.51 ng/mL and the NPY level 2.95±2.00 ngl/mL (15).

Cord blood sample leptin level in one study was 23.44 ng/mL, compared to 7.82 ng/mL in an adult control group (mean age 26.73 years) (16). Leptin levels were measured in constitutional delayed puberty and in normal puberty. Mean leptin level in constitutional delay of puberty was 13.1±2.0 ng/mL and mean leptin level in normal puberty was 13.0±1.8 ng/mL (mean age 16.1 years). The mean NPY level in constitutional delay of puberty was 199.4±105.1 pg/mL and the mean NPY level in normal puberty was 56.9±26.3 pg/mL (mean age 12.5 years) (17). In another study, leptin and NPY were examined initially and a mean 7.21±2.32 months after treatment in patients with anorexia nervosa. Mean leptin concentration increased from 7.99±2.6 to 9.98±2.48 μg/mL, whereas mean NPY concentration decreased from 34.10±9.81 to 29.6±8.04 pmol/L. These data were statistically significant (18). Leptin levels studied between the 3rd and 90th days of life increased significantly in both male and female newborns. There was no significant difference in the leptin levels and leptin/body mass index ratios in both the sex at different time points (19). We observed no correlation between weight, length, and body mass index and leptin or NPY.

Although several studies have investigated levels of leptin and NPY in children, studies involving newborns are very limited. One study compared serum leptin between twin and singleton infants and reported that serum leptin concentrations in twins (1.13±0.35 ng/mL) were significantly lower than those in the singleton infants (4.27±0.63 ng/mL) (20). In another study investigating the relationship between serum leptin levels and hematological parameters at birth, no correlation was determined between leptin and hemoglobin, leukocyte or platelet count at birth. Leptin levels in that study were 1.63±1.09 (21). In another study of 30 healthy full-term newborns, plasma leptin and plasma NPY levels were compared to umbilical cord blood concentrations. Mean cord blood

leptin value was 9.58±4.98 ng/mL and mean cord blood NPY was 44.47±19.35 pmol/L, whereas on the 4th day of life mean leptin was 4.91±6.06 ng/mL and mean NPY was 74.25±29.22 pmol/L. The authors emphasized the significant decrease in plasma leptin concentrations and the increase in plasma NPY concentrations (22). Cord blood leptin levels do not differ in terms of sex or body mass index (23, 24). However, there are studies reporting a relationship between cord blood leptin levels and birth weight (5, 8). In our study, no correlation was determined between weight, length, or body mass index, and serum leptin levels.

Another newborn study examined only leptin levels. The mean plasma leptin concentration in high gestational age infants was 4.83±1.84 ng/mL (range 1.69–8.46), 2.29±0.52 ng/mL (range 1.57–3.30) in average gestational age infants, and 2.23±0.75 ng/mL (range 1.22–3.96) in low gestational age infants. Significant differences were observed in mean leptin concentrations between high and average gestational age infants. However, no significant differences in terms of mean leptin concentrations were observed between low and average gestational age infants (25).

The limitations of this study are the small sample size and that the overall neonatal period was not included.

We determined mean leptin levels of 4.25±3.08 and 3.49±2.52 ng/mL and mean NPY levels of 24.79±9.87 and 25.80±9.58 ng/mL in our 14- to 28-day-old female and male newborns, respectively. In conclusion, leptin and NPY levels in the neonatal period do not differ in terms of sex.

Conflict of interest statement

Funding: No funding
Financial disclosure statement: The authors have no financial disclosures relevant to this article.
Conflict of interest statement: The authors have no conflicts of interest relevant to this article to disclose. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
Clinical trial registry name and registration number: None
Authors' contribution:
Avni Kaya: Manuscript preparation, patient's doctor, data acquisition, literature research, approved the final manuscript as submitted.
Zerrin Orbak: Patient's doctor, manuscript editing, approved the final manuscript as submitted.
İsmail Polat: Patient's doctor, data acquisition, approved the final manuscript as submitted.
Harun Polat: Biochemical analysis, approved the final manuscript as submitted.
Musa Gümüşdere: Biochemical analysis, approved the final manuscript as submitted.

References

1. Schwartz MW, Seeley RJ, Campfield LA, Burn P, Baskin DG. Identification of targets of leptin action in rat hypothalamus. J Clin Invest 1996;98:1101–6.
2. Yüksel B. Neuroendocrinological control of obesity. J Clin Res Ped Endo 2009;1:58–64.
3. Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obes Rev 2007;8:21–34.
4. Rosenbaum M, Leibel RL. Leptin: a molecule integrating somatic energy stores, energy expenditure and fertility. Trends Endocrinol Metab 1998;9:117–24.
5. Schubring C, Siebler T, Kratzsch J, Englaro P, Blum WF, et al. Leptin serum concentrations in healthy neonates within the first week of life: relation to insulin and growth hormone levels, skinfold thickness, body mass index and weight. Clin Endocrinol 1999;51:199–204.
6. Kratzsch J, Schubring C, Stitzel B, Bottner A, Berthold A, et al. Inverse changes in the serum levels of the soluble leptin receptor and leptin in neonates: relations to anthropometric data. J Clin Endocrinol Metab 2005;90:2212–7.
7. Kratzsch J, Hockel M, Kiess W. Leptin and pregnancy outcome. Curr Opin Obstet Gynecol 2000;12:501–5.
8. Schubring C, Kiess W, Englaro P, Rascher W, Dotsch J, et al. Levels of leptin in maternal serum, amniotic fluid, and arterial and venous cord blood: relation to neonatal and placental weight. J Clin Endocrinol Metab 1997;82:1480–3.
9. Hashimoto R, Udagawa J, Kagohashi Y, Matsumoto A, Hatta T, et al. Direct and indirect effects of neuropeptide Y and neurotrophin 3 on myelination in the neonatal brains. Brain Res 2011;1373:55–66.
10. Bouret SG, Draper SJ, Simerly RB. Trophic action of leptin on hypothalamic neurons that regulate feeding. Science 2004;304:108–10.
11. Bianco SD. A potential mechanism for the sexual dimorphism in the onset of puberty and incidence of idiopathic central precocious puberty in children: sex-specific kisspeptin as an integrator of puberty signals. Front Endocrinol 2012;3:149.
12. Argente J, Barrios V, Chowen JA, Sinha MK, Considine RV. Leptin plasma levels in healthy Spanish children and adolescents, children with obesity, and adolescents with anorexia nervosa and bulimia nervosa. J Pediatr 1997;131:833–8.
13. Lavoie HB, Taylor AE, Sharpless JL, Anderson EJ, Strauss CC, et al. Effects of short-term hormone replacement on serum leptin levels in postmenopausal women. Clin Endocrinol 1999;51:415–22.
14. Doniec Z, Pierzchala-Koziec K, Tomalak W, Kurzawa R. Serum level of leptin and neuropeptide Y in children with mild asthma. Pneumonol Alergol Pol 2004;72:9–13.
15. Saranac L, Bjelakovic B, Stamenkovic H, Kamenov B. Orexitropic signaling proteins in obese children. ScientificWorldJournal 2007;7:1263–71.

16. Pita J, Rado-Peralta S, Gavela-Perez T, Aragon I, Barrios V, et al. Plasma kisspeptin levels are elevated in cord blood and present sexual dimorphism in the adult population: relation with leptin, gonadotropins and anthropometrical data. Peptides 2011;32:983–8.
17. Blogowska A, Krzyzanowska-Swiniarska B, Zielinska D, Rzepka-Gorska I. Body composition and concentrations of leptin, neuropeptide Y, beta-endorphin, growth hormone, insulin-like growth factor-I and insulin at menarche in girls with constitutional delay of puberty. Gynecol Endocrinol 2006;22:274–8.
18. Oswiecimska J, Ziora K, Geisler G, Broll-Waska K. Prospective evaluation of leptin and neuropeptide Y (NPY) serum levels in girls with anorexia nervosa. Neuro Endocrinol Lett 2005;26:301–4.
19. Akcurin S, Velipasaoglu S, Akcurin G, Guntekin M. Leptin profile in neonatal gonadotropin surge and relationship between leptin and body mass index in early infancy. J Pediatr Endocrinol Metab 2005;18:189–95.
20. Onal EE, Uysal FK, Cinaz P, Bideci A, Dilmen U. Serum leptin levels in twins and singleton newborns. J Pediatr Endocrinol Metab 2003;16:733–9.
21. Koc E, Bideci A, Cinaz P, Ergenekon E, Atalay Y. Relationships between levels of leptin and hematological parameters in healthy term infants. J Pediatr Endocrinol Metab 2001;14:1129–32.
22. Mami C, Manganaro R, Marseglia L, Saitta G, Gemelli M, et al. Plasma leptin, insulin, and neuropeptide Y response to feeding in newborn infants. Arch Dis Child Fetal Neonatal Ed 2006;91:F389.
23. Schubring C, Englaro P, Siebler T, Blum WF, Demirakca T, et al. Longitudinal analysis of maternal serum leptin levels during pregnancy, at birth and up to six weeks after birth: relation to body mass index, skinfolds, sex steroids and umbilical cord blood leptin levels. Horm Res 1998;50:276–83.
24. Kirel B, Tekin N, Tekin B, Kilic FS, Dogruel N, et al. Cord blood leptin levels: relationship to body weight, body mass index, sex and insulin and cortisol levels of maternal-newborn pairs at delivery. J Pediatr Endocrinol Metab 2000;13:71–7.
25. Cinaz P, Sen E, Bideci A, Ezgu FS, Atalay Y, et al. Plasma leptin levels of large for gestational age and small for gestational age infants. Acta Paediatr 1999;88:753–6.