Plasma Kisspeptin Levels in Newborn Infants with Breast Enlargement

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Abstract

Objective: Kisspeptin levels have been reported in children with premature thelarche, precocious puberty and adolescent gynecomastia, but there are no reports on kisspeptin levels in the neonatal period. This study aimed to investigate plasma kisspeptin hormone levels in newborns with and without breast enlargement.

Methods: Plasma kisspeptin levels and other related biochemical variables were investigated in this prospective study conducted on 40 (20 girls and 20 boys) newborn infants with breast enlargement and on 40 healthy control infants (20 girls and 20 boys). Two-milliliter venous blood samples were taken in hemogram tubes with K2EDTA. Kisspeptin assays were performed using the enzyme-immunoassay method.

Results: Mean plasma kisspeptin levels were 0.6±0.2 ng/mL in the study group and 0.5±0.2 ng/mL in the control group. Plasma kisspeptin concentrations were significantly higher in the study group (p=0.039) and also showed a correlation with serum prolactin levels (p=0.006). Significant correlations were also determined between plasma kisspeptin and luteinizing hormone concentrations (p=0.05, r=0.312).

Conclusion: The findings of this study suggest that plasma kisspeptin and serum prolactin levels may be involved in the physiopathology of breast enlargement in newborns.

Key words: Kisspeptin, newborn, breast enlargement

Conflict of interest: None declared
Received: 12.03.2015 Accepted: 24.05.2015

Introduction

Kisspeptin is a powerful neuropeptide that stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary. It exhibits this effect through the gonadotropin-releasing hormone. Kisspeptin is synthesized in the anteroventral periventricular nucleus and the arcuate nucleus of the hypothalamus (1). A significant rise in FSH, LH and testosterone levels when kisspeptin is administered intravenously demonstrates its role in the hypothalamo-pituitary-gonadal axis (2). Kisspeptin is one of the peptides regulating the neuroendocrine events initiating puberty in humans and animals (3,4,5). Kisspeptin levels have previously been studied in premature thelarche, precocious puberty and in gynecomastia in adolescence, but to our knowledge, there are no reported studies on kisspeptin in breast enlargement in the neonate (6,7,8).

The aim of this study was to determine and compare kisspeptin levels in 14-28-day-old infants with and without breast enlargement.

Methods

This prospective study was performed on infants with and without breast enlargement who presented to the Pediatric Endocrinology Outpatient Clinic of the Atatürk University Faculty of Medicine Research Hospital in Erzurum, Turkey, between September 2013 and March 2014. The purpose and design of the study was explained to all the families and the requisite written consent was obtained.

Forty term infants (20 boys and 20 girls) aged 14-28 days with breast enlargement and 40 (20 boys and 20 girls) control infants without breast enlargement and of the same age group were included in the study. Criteria for
exclusion consisted of presence of congenital abnormality in the infant and/or chronic disease in the mother. Breast enlargement was evaluated on the basis of the breast diameter. Infants who showed breast enlargement of more than 1 cm in diameter were included in the study. Infants without breast enlargement constituted the control group.

Following receipt of informed consent, prenatal and postnatal histories including week of gestation at birth, age, type of delivery (cesarean section delivery or vaginal delivery) and type of feeding (mother’s milk and/or formula) were taken from the mothers and physical examination was conducted on the infant. The infant’s age, length, body weight, breast stage and testis volume (using a Prader orchidometer) were recorded. Apart from breast enlargement, physical examination was normal in all infants. Blood samples were collected from all babies for measurement of FSH, LH, estradiol, testosterone, prolactin, free thyroxine (fT4) and thyroid-stimulating hormone (TSH). Kisspeptin levels were determined on blood samples which were collected from the infants with breast enlargement, physical examination was normal in all infants. Blood samples were collected from all babies for measurement of FSH, LH, estradiol, testosterone, prolactin, free thyroxine (fT4) and thyroid-stimulating hormone (TSH). Kisspeptin levels were determined on blood samples which were collected from the infants with breast enlargement and controls in K EDTA hemogram tubes and centrifuged at +4 °C to separate blood cells and plasma. These were placed in Eppendorf tubes and stored at -80 °C until the acquisition of kisspeptin kits (KiSS-1 (112-121) Amide/Kisspeptin-10/Metastin (45-54) Amide (Human) EIA KIT, Phoenix Pharmaceuticals Inc., USA, Catalog No: EK-048-56, Lot No: 604601). Plasma kisspeptin levels were measured, following the manufacturer’s instructions, using the enzyme-immune assay (EIA) technique at the Atatürk University Hospital Department of Biochemistry. Kisspeptin levels were expressed as nanograms/milliliter.

Numerical data were expressed as minimum, maximum, mean and standard deviation. Other data were expressed as percentages. SSPE 20 for Windows was used for data analysis. The one-sample Kolmogorov-Smirnov test was used to determine whether numerical data in the thelarche and control groups were normally distributed.

The infants’ body weight, length, postnatal ages, body mass index, LH, testosterone, prolactin, fT4, TSH and kisspeptin levels were normally distributed according to the one-sample Kolmogorov-Smirnov test. The independent-sample t-test was used to analyze these data. FSH, estradiol levels and FSH/LH ratio were not normally distributed according to the one-sample Kolmogorov-Smirnov test. The nonparametric two-independent-samples Mann-Whitney U test was used to analyze these data. Type of delivery, feeding status and testis size were determined using the Pearson’s chi-square test. Statistical significance was considered at p<0.05.

The study was approved by the local ethics committee (Atatürk University Faculty of Medicine Ethics Committee on September 2, 2013, Session 6, Item 62).

Results

Mean age of the cases in the breast enlargement group was 20.6±4.1 days (14-27 days). Mean body weight was 4.1±0.6 kg (3.3-5.8 kg) and length 52±1.7 cm (49-57 cm). Twenty-nine (72.5%) patients were delivered vaginally and 11 (27.5%) by cesarean section. Thirty-five (87.5%) patients were receiving mother’s milk and 5 (12.5%) mother’s milk supplemented by formula. No subject was on formula alone. Testis volume was measured as 1 mL in 6 male patients (30%), 2 mL in 12 (60%) and 3 mL in 2 (10%). Laboratory values of the breast enlargement cases are shown in Table 1. Normal ranges accepted for the biochemical parameters were: FSH male: 0.2-4.1 mIU/mL, female: 0.2-14.2 mIU/mL, LH: 0.0-7.0 mIU/mL, estradiol male: 0.1-32 pg/mL, female: 0.1-50 pg/mL, testosterone total, male: 0.075-4 ng/mL, female: 0.0-0.64 ng/mL, prolactin 30-495 ng/dL, fT4: 0.6-1.4 ng/dL, thyroid TSH: 0.6-7 μIU/mL.

Mean age in the control group was 21.6±4.2 days (14-28 days), body weight 3.9±0.6 kg (3.5-5.5 kg) and length was 51.5±2.0 cm (46-55 cm). Twenty-three (57.5%) of the cases in the control group were delivered vaginally and 17 (42.5%) by cesarean section. Thirty-three (82.5%) were receiving mother’s milk and 7 (17.5%) were on mother’s milk and formula. No babies were on formula alone. Testis volume in male subjects was 1 mL in 10 (50%) and 2 mL in 10 (50%). Laboratory values for the control group cases are shown in Table 1.

Minimum, maximum, mean and standard deviation kisspeptin values as well as p-values by sex and breast enlargement are shown in Table 2.

There was a significant difference in kisspeptin levels between the study and control groups (p=0.039). These groups also differed significantly in terms of prolactin concentrations (p=0.006). No significant correlation was determined of breast enlargement with body weight (p=0.319), length (p=0.228), body mass index (p=0.683), postnatal age (p=0.283), LH (p=0.309), testosterone (p=0.619), fT4 (p=0.968), TSH (p=0.419), FSH (p=0.453), estradiol (p=0.817) and FSH/LH ratio; breast enlargement was not associated with type of delivery (p=0.16) or type of nutrition (p=0.531) as well.

A significant correlation was determined between kisspeptin levels and LH (p=0.05, r=-0.312). Correlation analysis data in the breast enlargement and control groups are shown in Table 3.

Discussion

Minipuberty occurs in all infants in the newborn period. The release of kisspeptin in the neonatal period may possibly be related to the activation of the hypothalamic-pituitary-gonadal axis in this period of life. Various studies
have examined kisspeptin levels in children and adults, but
our scan of the literature revealed no studies investigating
plasma kisspeptin levels in infants with breast enlargement in
the newborn period.

Studies have reported that kisspeptin levels in the
circulation are sexually dimorphic in humans, with kisspeptin
levels in females being significantly higher than in males
(9,10,11,12,13,14). In our study also, mean kisspeptin levels in
infants without breast enlargement were slightly higher in the
girls. Mean kisspeptin levels in the female infants with breast
enlargement were also significantly higher as compared to the
boys.

Plasma kisspeptin levels in different studies have been
reported at 3.0±1.2 ng/dL in children aged 3-8 years (8),
Kisspeptin has also been shown to be a powerful LH secretion stimulator and to lead to an increase in LH levels in males and females (2,16,17,18). Similarly, in girls, a positive correlation has been determined between serum kisspeptin levels and development of puberty and also between kisspeptin levels and bone age, LH and LH/FSH ratio (6). Another study reported that kisspeptin increased FSH release seven times more compared with LH (17). According to another study, in order to establish a significant increase in serum FSH, a dose 100 times higher than that required to increase LH needed to be given (19). In our study, a significant correlation was found between plasma kisspeptin and LH levels (p=0.050).

In conclusion, the results of this study suggest that plasma kisspeptin and serum prolactin levels may be involved in the physiopathology of breast enlargement in newborns.
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