No association between serum level of NPTX 1 and MKRN3 in central precocious puberty

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Abstract

Background: Makorin ring finger protein 3 (MKRN3) is most common genetic cause of central precocious puberty (CPP) and associated with the initiation of puberty. Although its actual function is veiled. Recent study reported MKRN3 interacted with and suppressed neural pentraxin-1 precursor (NPTX1) activity via polyubiquitination during early puberty in mice.
Objective: The aim of this study was to investigate the correlation between serum NPTX 1 and MKRN3 in CPP girls.
Methods: In this case-control study, we examined 38 girls referred for early breast development (before the age of 8 years). The control group included healthy and prepubertal girls. Anthropometric and hormonal parameters were measured and serum level of NPTX1 and MKRN3 were evaluated by commercial ELISA kit.
Results: Serum MKRN3 level was significantly higher in CPP patients than controls(p < 0.001). In patients, serum NPTX1 level was measured higher than control, there was no statistical difference (p = 0.228). Also, serum NPTX 1 was positively correlated with peak LH (r = 0.338, p <0.05), there was no correlated between NPTX1 and MKRN3 in CPP girls(p = 0.882).
Conclusion: Serum MKRN3 decrease and NPTX1 tends to increase in CPP girls. Although, serum NPTX1 and MKRN3 have no significant association, they are likely to be involved in the onset and regulation of puberty.

Introduction

Central precocious puberty is caused by early maturation of the hypothalamic-pituitary-gonadal axis, resulting in pulsatile secretion of GnRH and subsequent activation of the gonads.
Paternally inherited loss-of-function mutations in MKRN 3 as a most common genetic cause of central precocious puberty suggests a pivotal role for MKRN3 in the transrepression of sexual maturation, but the exact mechanism remains unclear. MKRN3 protein has 4 zinc finger domains namely 3 C3H1 motifs and 1 C3H4 Ring finger with presumed E3 ubiquitin ligase activity. Although Mkrn3 is postulated to be an inhibit stimulator of GnRH secretion, however, the molecular mechanism of MKRN3 effect on GnRH network still remains unclear.
Nptx1, which is observed highly expressed in hypothalamus when puberty onset and plays an important role in neural differentiation. Chen et al reported, hypothalamic Mkrn3 expressed the reversed tendency with Nptx1, which is an important secreted protein for neuron development and Mkrn3 interacted and suppressed Nptx1 activity in mice.
In this study, we investigated the correlation between serum MKRN3 and NPTX1 level in girls with central precocious puberty.

Subjects and Methods

Subjects

Thirty eight girls with idiopathic CPP aged 7.0-8.9 years and 34 age-matched prepubertal girls who visited the Pediatric Endocrinology Department at the Hallym Medical Center for their growth checkup between March 1, 2013 and August 31, 2015 were enrolled. The patients all exhibited breast enlargement appearing before the age of 8 years. Bone ages (BA) were found to be at least 1 year ahead of the patients' chronological age. A GnRH stimulation test was carried out in all patients to confirm that the HPG axis had been activated, as revealed by peak luteinizing hormone (LH) levels ≥ 5.0 IU/L on a chemiluminescent microparticle immunoassay
Inclusion criteria for the normal control group were follows: no evidence of breast budding and BA - CA < 1 year. All blood samples were centrifuged, and serum was separated and stored at -80'C before it was assayed.

Methods

Data on height, weight, BMI, pubertal status, and bone age were collected every 6months from clinical charts and electronic medical records. This study protocol was approved by the Institutional Review Board of the Hallym Medical Center (KANGDONG 2016-11-003).

Serum LH, FSH, and estradiol (E_2) were measured only in the patient group. Serum MKRN3 concentrations were determined using a commercially available Human MKRN3 ELISA Kit (MyBioSource, San Diego, CA, USA),with a detection limit of 7.8 pg/mL. The intra- and inter-assay coefficients of variation (CVs) listed by the manufacturer were < 8% and < 12%, respectively. The test worked as stated by the manufacturer. Serum NPTX1 levels were determined using a commercially available Human MKRN3 ELISA Kit (MyBioSource, San Diego, CA, USA). with a detection limit of 0.10ng/mL. The intra- and inter-assay coefficients of variation (CVs) listed by the manufacturer were < 10%, respectively.

Statistics

The endocrine parameters of the patients and controls were compared by Student's *t*-tests. The correlations between MKRN3 and endocrine parameters were evaluated using Pearson's correlation coefficient. All values are expressed as the mean ± SD. *P*-values < 0.05 were regarded as statistically significant. All statistical analyses were performed with the aid of SPSS (ver. 20.0; SPSS Institute, Chicago, IL, USA)

Results

Table 1. Baseline characteristics of the subjects.

	CPP patient (n=38)	Control (n=34)	*p* value
Age at diagnosis (year)	8.43 ± 0.47	8.32 ± 0.47	0.314
Ht SDS	1.33 ± 0.86	-0.16 ± 0.65	0.000
Wt SDS	1.19 ± 0.74	-0.11 ± 0.84	0.000
BMI SDS	0.84 ± 0.77	-0.08 ± 1.03	0.000
BA – CA (year)	2.01 ± 0.75	-0.21 ± 0.77	0.000
Tanner (breast)	2.50 ± 0.50	1.17 ± 0.38	0.000
Basal LH (IU/L)	1.38 ± 1.11	-	ns
Basal FSH (IU/L)	3.26 ± 1.79	-	ns
Peak LH (IU/L)	10.94 ± 5.12	-	ns
Peak FSH (IU/L)	17.00 ± 7.46	-	ns
MKRN3(pg/mL)	529.27 ± 630.44	1319.49 ± 771.39	0.000
NPTX1 (ng/mL)	19.16 ± 30.16	12.68 ± 7.69	0.228

Table 2. The correlation between NPTX1 and endocrinological parameters in 38 girls with CPP.

	r	*p value*
Age (years)	-0.275	0.094
BA (years)	0.261	0.114
Tanner stage	0.243	0.142
Height SDS	0.308	0.060
Weight SDS	0.197	0.236
BMI SDS	–0.15	0.193
Basal LH (IU/L)	0.036	0.831
Basal FSH (IU/L)	0.141	0.399
Peak LH (IU/L)	0.338	0.038
Peak FSH (IU/L)	0.098	0.559
E_2 (pg/mL)	-0.057	0.734
MKRN3	-0.025	0.882

Conclusions

Serum MKRN3 decrease and NPTX1 tends to increase in CPP girls. Serum concentrations of NPTX1 were not significantly associated with MKRN3, therefore, it is difficult to estimate the interaction between the two. However, NPTX1 has a positive correlation with peak LH in CPP girls, which is likely to be related to the onset and regulation of puberty. A larger prospective study is warranted to confirm these initial exploratory results.

The authors have no conflicts of interest to declare