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Changes in circadian rhythm of prolactin in short children are dependent on growth hormone secretion

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Abstract

Introduction and objective. Taking into consideration the common ontogenic origin of prolactin (Prl) and growth hormone (GH), the Prl circadian pattern was analysed in children with different degrees of GH deficiency (GHD).

Materials and methods. The analysis comprised 100 short children (31 girls and 69 boys), aged: 10.1±3.51 years. Based on maximal GH secretion (GHmax) during two stimulating tests multiple hormone deficiency (MPHD), severe isolated GHD (SIGHD), partial isolated GHD (PIGHD) or idiopathic short stature (ISS) were diagnosed. Non-inferential chronobiometry (macroscopic analysis) of the circadian Prl rhythm, based on serum Prl measured every 3 hours during 24 hours, was performed. In this analysis, mesor, the area under curve (AUC), peak and trough level, dispersion, mean nocturnal and diurnal concentration, night/day ratio, amplitude and regression index were estimated.

Results. In the study group, the positive correlations between GHmax and Prl concentrations at 02:00 and at 05:00 were observed, as well as between GHmax and mesor, amplitude, mean nocturnal concentration, night/day ratio and AUC. The nocturnal rise of Prl secretion was blunted in 100% MPHD and 50% SIGHD children, whereas in most children with PIGHD and ISS, the circadian Prl rhythm was normal.

Conclusions. 1) In short children, the lower the concentration of GH is, the more blunted nocturnal Prl secretion becomes. 2) In the majority of MPHD and SIGHD children (but not PIGHD), the circadian Prl rhythm was disturbed; namely, reduced nocturnal Prl secretion was noticeable.

Key words

prolactin, circadian rhythm, growth hormone deficiency, children

INTRODUCTION

In normal conditions, prolactin (Prl) secretion in children (similarly as in adults) is characterized by circadian rhythmicity, with higher serum concentrations during the night hours and lower ones during the day [1,2]. Development of the pituitary gland is controlled by several transcription factors of the POU-homeodomain class, such as Ptx1, Ptx2, Hesx1 (Rpx) and LIM-dependent proteins (P-LIM, Lhx3 and Lhx4). After Rathke's cleft formation, PROP-1 (Prophet of Pit-1) turns off expression of the *Hesx1* gene, switching on expression of the *Pit-1* gene, which in turn affects the differentiation of lactotrophs, somatotrophs and the early subpopulation of thyrotrophs [3,4]. Thus, the mutations in these genes are responsible for disorders of pituitary cells differentiation [5]. In our previous work, it was proved that in children with growth hormone (GH) deficiency (GHD) and congenital organic lesions in the hypothalamo-pituitary region, nocturnal Prl increase is blunted in the majority, but not in all patients [6].

On the other hand, there are some substances which stimulate production of both hormones, for example, ghrelin. It is possible that their dysregulation is responsible for the lower production of GH and Prl from the pituitary, independent of organogenesis disorders [7,8]. The aim of the presented study was to evaluate the circadian rhythm of Prl secretion in children with different degrees of GH deficiency, in comparison to idiopathic short stature (ISS) children, demonstrating normal GH secretion.

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MATERIALS AND METHODS

The study comprised 100 children with short stature (31 girls and 69 boys), their age ranged from 5.2 – 14.8 years (mean age ±SD: 10.1±3.51 years). Children with chronic diseases, especially concerning the gastrointestinal tract and/or the urinary system, were excluded from the study. During the period of examinations, none of the children revealed any signs of infection.

The study was approved by the Bioethical Committee of the Polish Mother's Memorial Hospital – Research Institute (PMMH-RI). The experimental protocol was explained to each patient's parents and an informed consent was obtained.

Auxological studies. In each child, the actual body weight and height were measured. Based on the obtained values, the height standard deviation score (HSDS) and the body mass index standard deviation score (BMISDS) for age and gender were calculated. The children were qualified into the study if HSDS was below -2.0.

Hormonal assessment. In each individual, routine laboratory examinations were performed within the diagnostics of short stature during hospitalisation at the Department of Endocrinology and Metabolic Diseases of PMMH-RI in Lodz.

In each child, TSH, FT4, IGF-I, IGF BP3 and morning cortisol concentration were assessed. In girls, Turner's syndrome was excluded by genetic assessment. In children with delayed puberty (lack of signs of puberty after age 13 in girls and after age 14 in boys), LH and FSH (during stimulating test with gonadoliberin) and estradiol or testosterone concentrations were assessed in order to exclude primary LH and FSH deficiency (hypogonadotropic hypogonadism).

In children with TSH and/or ACTH deficiency, GH and IGF-I secretion was evaluated after normalization of thyroxine and hydrocortisone concentrations, with application of an appropriate substitution treatment. IGF-I concentrations were expressed by IGF-I SDS for gender and chronological age (CA), according to reference data (IGF-I SDS for CA). GH serum concentrations were measured during two GH stimulating tests: at 0, 30, 60, 90, 120 minutes, following clonidine administration orally (0.15 μg/m^2 body area) and at 0, 90, 120, 150, 180 minutes, following intramuscular glucagon administration (30 μg/kg body mass, maximal 1,000 μg).

Growth hormone concentrations were estimated using the immunometric method (IMMULITE, DPC, sensitivity – 0.01 ng/ml, intraassay coefficient variability (CV) – 5.3–6.5%, interassay CV – 5.5–6.2%).

Based on the maximal GH values (GHmax) obtained in two GH stimulation tests, and deficiency of other pituitary hormones, the children were divided into four groups:

1) MPHD – multiple hormone deficiency group, including GH (n=8);
2) SIGHD – severe isolated GHD group (n=15; GHmax below 5 ng/ml);
3) PIGHD – partial isolated GHD group (n=36; GHmax above 5 ng/ml but below 10 ng/ml);
4) ISS – idiopathic short stature group (n=41, GHmax above 10 ng/ml).

Estimation of prolactin concentration. In each child, the profile of Prl circadian secretion was determined on the basis of Prl concentrations in serum, measured every three hours during 24 hours. Blood samples were collected at 08:00, 11:00, 14:00, 17:00, 20:00, 23:00, 02:00, 05:00 and 08:00. All blood samples were left to clot for 45 minutes; serum was removed after centrifugation, and stored at -20°C until assay. Prl concentrations were measured by the electrochemiluminescence method (ELISA, Roche, Elecsys®Systems, its sensitivity was 0.47 ng/ml, in the range up to 470 ng/ml, the inter-assay CV was 1.8–3.4%).

Based on the measured Prl concentrations during 24 hours, the following circadian rhythm parameters were calculated (macroscopic analysis) [9]:

- mesor (the overall mean level);
- median;
- area under the curve (AUC);
- peak level (the maximal Prl concentration);
- trough level (minimal Prl concentration);
- dispersion (differences between maximal and minimal concentrations);
- amplitude (peak level and mesor ratio);
- mean nocturnal concentration (Xn), (mean Prl concentration from three night-time points: 23:00, 02:00 and 05:00);
- mean diurnal concentration (Xd), (mean Prl concentration from three diurnal time points: 11:00, 14:00 and 17:00);
- Xn/Xd ratio;
- regression index (the directional index, i.e., index of the slope of the regression straight line in relation to the axis of ordinates).

On the basis of the results obtained from our previous work, the presence of normal circadian Prl rhythm we recognised, if at least one of the following three criteria were fulfilled: amplitude more than 1.8779; Xn/Xd ratio more than 1.685; regression index below 0.4107 [10].

MR examination. MR examination was performed in all patients with GHD and the presence of organic abnormalities evaluated. The pituitary height (PtH) was determined in the antero-posterior projection by measuring the greatest distance between the superior and inferior borders of the gland. Pituitary hypoplasia was diagnosed when the value of the pituitary height was below -2.0 standard deviation from the mean value for age and gender, using the standards developed by Argyropoulou et al. in 1991 [11]. If – additionally to pituitary hypoplasia – invisible neurohypophysis or it ectopia and/or thinned or completely invisible pituitary stalk were found in MR examination, the pituitary stalk interruption syndrome (PSIS) was diagnosed. In some children, microadenoma of hypophysis (diameter of adenoma less than 10 mm) was recognised. The results of MR examination in particular analyses groups of children are presented in Table 1.

Table 1. Number of children with different results of MR examination with respect to hormonal diagnosis (partial or severe isolated growth hormone deficiency and multiple pituitary hormone deficiency)

	MPHD	SIGHD	PIGHD	Together
NORM	0	3	22	25
HYPO	3	7	7	17
PSIS	5	6	0	11
INC	0	0	6	6
Total	8	16	35	59

MPHD – multiple pituitary hormone deficiency
SIGHD – severe isolated growth hormone deficiency
PIGHD – partial isolated growth hormone deficiency
NORM – normal pituitary gland without organic abnormalities visible in MR examination
PSIS – pituitary stalk interruption syndrome
INC – incidentaloma (no functioning microadenoma of hypophysis)
HYPO – pituitary hypoplasia

Statistical analysis. The data were statistically analysed using the one-way analysis of variance (ANOVA), followed by *post-hoc* testing of the differences of means (RIR Tukey test). In certain cases, the non-parametric Kruskal-Wallis test was used for a screening evaluation of the differences of means. Statistical significance was determined at the level p below 0.05.

RESULTS

The chronological age of children and their BMISDS values were not different among the groups; however, the height of children (expressed by HSDS) was significantly lower in MPHD group than in PIGHD and in ISS group (auxological and hormonal data in particular groups of children are

Table 2. Mean values (±SD) of chronological age (CA), height deficiency (HSDS), body mass index (BMISDS), and hormonal examinations results in particular groups of children

	GHD			ISS
	MPHD	SIGHD	PIGHD	
No. of children (boys/girls)	8 (6/2)	15 (10/5)	36 (28/8)	41 (25/16)
CA (years)	9.5 ± 3.50	11.48 ± 4.32	11.88 ± 3.16	11.45 ± 3.20
HSDS	-3.46 ± 1.11 [a,b]	-2.66 ± 0.71	-2.28 ± 0.35 [a]	-2.21 ± 0.65 [b]
BMISDS	-0.11 ±1.49	-0.33 ± 1.45	-0.94 ± 1.51	-0.89 ± 1.18
GHmax (ng/ml)	2.34 ± 2.95 [c,d]	3.24 ± 2.21 [e]	8.12 ± 2.34 [c]	17.0 ± 6.21 [d,e]
IGF-ISDS for CA	-3.28 ± 2.33 [f,g,h]	-0.82 ± 1.57 [f]	-0.30 ± 1.20 [g]	-0.34 ± 1.52 [h]

a–h: p < 0.05
MPHD – multiple pituitary hormone deficiency
SIGHD – severe isolated growth hormone deficiency
PIGHD – partial isolated growth hormone deficiency
ISS – idiopathic short stature
CA – chronological age
HSDS – standard deviation score for patient's height
GHmax – maximal concentration of growth hormone in stimulating tests
IGF-I SDS for CA – standard deviation score of insulin-like growth factor type I for chronological age

presented in Table 2). In the entire analysed group of children, positive correlations between GHmax and Prl concentrations at 02:00 (r=0.41; p<0.05) (Fig. 1) and at 05:00 h (r=0.36; p<0.05) were observed. Moreover, the correlation between GHmax and Prl mesor (r=0.27; p<0.05), Prl amplitude (r=0.36; p<0.05), Xn – the mean nocturnal Prl concentration (r=0.35; p<0.05), Xn/Xd ratio (r=0.35; p<0.05), as well as the area under the curve of Prl concentration (r=0.24; p<0.05) were noted, indicating a relationship between the functional reserve of the pituitary gland in secretion of GH and nocturnal (but not diurnal) Prl secretion.

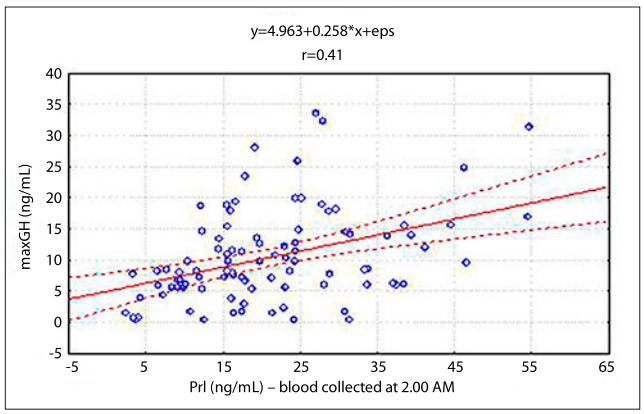

Figure 1. Correlation between GH_{max} concentrations and Prl concentrations at 2.00 in entire group of children

Table 3. Values (± SD) of prolactin (Prl) concentrations at each time point in particular groups of children

Time point	GHD			ISS
	MPHD	SIGHD	PIGHD	
	Prl (ng/ml)			
8:00	9.51 ± 7.87	13.92 ± 8.36	12.98 ± 6.64	15.56 ± 10.74
11:00	7.50 ± 5.72	8.91 ± 6.49	6.24 ± 4.87	9.75 ± 4.31
14:00	7.96 ± 6.40	9.21 ± 6.57	8.04 ± 4.47	9.90 ± 5.04
17:00	7.95± 6.24	8.93 ± 4.69	8.35 ± 4.58	9.13 ± 5.91
20:00	8.70 ± 7.72	9.40 ± 4.36	10.39 ± 8.99	10.24 ± 6.70
23:00	11.35 ± 13.29	11.80 ± 5.75	12.42 ± 11.63	13.01 ± 10.31
2:00	11.14 ± 10.26 [a]	15.07 ± 7.37 [b]	20.38 ± 11.49	25.69 ± 11.05 [a,b]
5:00	8.86 ± 6.84 [c]	14.81 ± 7.44	16.00 ± 8.77	20.30 ± 9.28 [c]
8:00′	8.88 ± 6.91	13.38 ± 9.35	12.05 ± 6.15	15.73 ± 10.34

a,b,c: p < 0.05
GHD – growth hormone deficiency
MPHD – multiple pituitary hormone deficiency
SIGHD – severe isolated growth hormone deficiency
PIGHD – partial isolated growth hormone deficiency
ISS – idiopathic short stature

Analysis of Prl concentrations at each time point in particular groups of children revealed that in the MPHD group and in the SIGHD group the nocturnal increase of Prl secretion (at 02:00 and 05:00) was significantly blunted, when compared to the ISS group (Tab. 3); the chronograms for each group are presented on Figure 2. Moreover, Xn value, dispersion and amplitude were significantly lower in MPHD and SIGHD than those in the PIGHD and ISS groups, while Xd and trough (minimal) level did not differ among all the groups, indicating normal Prl concentration during the day in MPHD and SIGHD groups (Tab. 4).

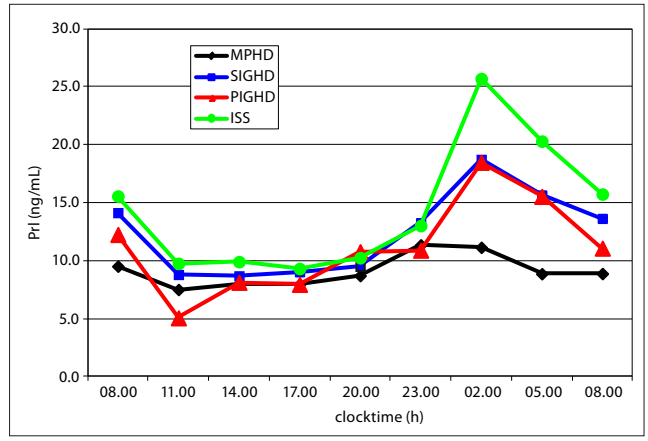

Figure 2. Chronograms of particular groups of the analysed children

Table 4. Values of estimated parameters of prolactin (Prl) rhythm in particular analysed groups

	GHD			ISS
	MPHD	SIGHD	PIGHD	
Mesor (ng/ml)	9.09 ± 7.70	11.71 ± 5.44	11.87 ± 4.63	14.39 ± 4.43
Median (ng/ml)	8.81 ± 7.23	10.68 ± 5.29	9.65 ± 4.06	11.62 ± 5.03
AUC (ng/ml/24 hours)	244.7 ± 209.55	314.42 ± 139.33	334.56 ± 132.94	367.05 ± 114.84
Peak level (ng/ml)	12.55 ± 13.18[a]	18.94 ± 9.13[b]	26.38 ± 11.71	31.26 ± 12.74[a,b]
Trough level (ng/ml)	6.84 ± 5.27	6.87 ± 4.84	4.53 ± 2.50	5.75 ± 2.48
Dispersion (ng/ml)	5.71 ± 9.0[c,e]	12.06 ± 8.34[d]	21.85 ± 10.17[c]	25.51 ± 12.79[d,e]
Amplitude	1.27 ± 0.23[f,g]	1.65 ± 0.39[h,i]	2.22 ± 0.44[f,h]	2.16 ± 0.51[g,i]
Xd (ng/ml)	7.80 ± 5.99	9.02 ± 5.32	7.55 ± 3.86	9.65 ± 4.65
Xn (ng/ml)	10.45 ± 9.87	13.89 ± 6.23	16.26 ± 8.50	19.67 ± 6.43
Xn/Xd ratio	1.26 ± 0.27	1.79 ± 0.75	2.47 ± 1.21	2.43 ± 1.26
Regression index	-0.01 ± 0.16	-0.25 ± 0.24	-0.37 ± 0.47	-0.63 ± 0.69

a–i: p< 0.05
MPHD – multiple pituitary hormone deficiency
SIGHD – severe isolated growth hormone deficiency
PIGHD – partial isolated growth hormone deficiency
ISS – idiopathic short stature
AUC – area under the curve
Xn – the mean prolactin nocturnal concentration
Xd – the mean diurnal prolactin concentration

In the PIGHD group and ISS groups, in most of cases the Prl rhythm was normal, whereas in the majority of cases in the SIGHD and MPHD groups, the Prl rhythm was blunted. Disturbances of the Prl rhythm were observed in 100% of children with MPHD, in 50% children with SIGHD, but in 5.7% with PIGHD and in 7.3% with ISS, only.

Summing up, in children with MPHD and SIGHD, Prl concentrations were normal during the day; however, Prl levels during the night hours were reduced, whereas in children with PIGHD and ISS, normal Prl concentrations – both during the day and during the night – were observed.

DISCUSSION

The most interesting aspect of the presented study is providing evidence of differences in Prl circadian secretion patterns in children with GHD, depending on the degree of GH deficiency (PIGHD and SIGHD) and revealing the positive correlation between functional pituitary reserve in secretion of GH and nocturnal (but not diurnal) Prl secretion.

It seems that in children with severe isolated GHD, there are unfavourable conditions of Prl increased secretion during night hours. Thus, in fact, it is not only isolated GHD, but GHD together with partial Prl deficiency; i.e. it is possible that after falling asleep the production of both hormones in question is impaired. It depends on the factors, the nature of which remains to be elucidated.

In 2010, Lanfranco et al. [7] reported the influence of ghrelin on pituitary hormones other than GH. The authors showed that ghrelin significantly stimulates Prl secretion in humans, independently of both gender and age. Moreover, ghrelin probably exerts a direct action on somatomammotroph cells. Our previous report [12] also been proved that in children with GHD, ghrelin concentration is higher than in control and ISS groups. Despite high ghrelin concentrations, GH secretion was decreased in those cases. The mechanisms responsible for these phenomena are not yet sufficiently explained.

In the presented study, subjects with organic changes in the pituitary region, especially anterior lobe hypoplasia, thinning of the stalk and the ectopic posterior lobe were not included. We have previously confirmed [6] that in some GHD patients with pituitary hypoplasia, the normal circadian Prl profile is observed, whereas in others the Prl profile is disturbed. It is presumably dependent on the type of mutation, which is responsible for hypoplasia. It is well known that the mutations in GHRH receptor gene are responsible for pituitary hypoplasia and GHD, whereas Prl concentrations are within normal range, with the presence of circadian rhythm [13]. Mutations in *Pit-1* or *PROP-1* genes are related to pituitary hypoplasia with GHD and with low concentration of Prl, the secretory pattern of the latter hormone maybe normal or blunted [14,15]. The mutations in *Hesx1* gene lead to pituitary hypoplasia and subsequent deficiency of GH, TSH, LH, FSH and ACTH, while Prl concentration is normal, with occurrence of circadian rhythm [16, 17]. Thus, pituitary hypoplasia does not mean simultaneous presence of disorders of nocturnal Prl secretion. On the other hand, the normal anatomical connections between the hypothalamus and the pituitary gland, with normal tuberoinfundibular dopaminergic neurons, tuberohypophyseal dopaminergic neurons, the median eminence, the stalk and the *pars tuberalis* are necessary for appropriate regulation of Prl and GH secretion. In turn, in the case of PSIS, hyperprolactinemia may be observed due to the lack of dopaminergic inhibition caused by the disorders of anatomical connection between hypothalamus and pituitary. However, this disturbation is not observed in all patients as the degree of pituitary hypoplasia is different in particular cases of PSIS. Moreover, the genetic background of PSIS is heterogenous [18,19]. Thus, the inclusion into the study group of both the patients with organic abnormalities and those without that pathology in the hypothalamo-pituitary region seems justified. The relationships between GH secretion and nocturnal Prl secretion documented in the presented study may indicate the existence of other unclear interrelationships between these two hormones.

Further studies are therefore needed to determine the actual background of the above-mentioned observations.

According to current recommendations, the assessment of Prl concentration in a single blood sample is sufficient to diagnose hiperprolactinemia [20]. However, in our opinion, the assessment of Prl concentrations at several time points during the night should be performed to diagnose the course of circadian Prl rhythm, with blunted peak of Prl secretion during the night.

Summing up, in children with short stature, the lower the concentration of GH is, the more blunted nocturnal Prl secretion becomes. In the majority of children with MPHD and SIGHD (but not PIGHD), the circadian Prl rhythm was disturbed, i.e. reduced nocturnal Prl secretion was noticeable.

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