

Assessment of Physical Growth in Children with Congenital Adrenal Hyperplasia (CAH)

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Abstract

The study is an attempt to assess the degree and direction of deviations in two physical development traits: body weight and height in children with congenital adrenal hyperplasia (CAH), as compared to the norm. The pattern of growth of the studied traits in children with CAH is significantly different than an average pattern for normal children. A new research approach used to investigate the problem of developmental disorders in children with CAH revealed that both body height and weight – regardless of the sex – in successive stages (prepubertal, pubertal and postpubertal) of ontogenetic development tend to have progressively lower mean values as compared to the norm, and that differences between these values in the analyzed stages are statistically significant ($p < 0.01$).

Keywords: Congenital Adrenal Hyperplasia (CAH), growth disorder, level and trend of growth

Introduction

Congenital Adrenal Hyperplasia (CAH) is a genetically determined syndrome. It is directly associated with the occurrence of enzymatic blocks in the pathways of biosynthesis of adrenal cortex hormones (glucocorticoids and mineralocorticoids) [1, 2]. The most frequent cause of CAH is 21-hydroxylase deficiency. In 90-95% of cases the absence of this enzyme is a result of a mutation of CYP21 gene (6p21.3) [3-6]. There is a great genetic polymorphism at this locus which is manifested by varied phenotypic expression and hence a varied clinical presentation [5, 7-9]. Cases of deficiency of 17-hydroxylase, 11-hydroxylase and 3 β -hydroxysteroid dehydrogenase are less frequent. All these enzymes take part in the synthesis of the steroid hormones. Inadequate production of the steroid hormones of adrenal cortex disturbs the body's hormonal balance. As a result of a low level of cortisol produced by adrenal glands, the pituitary gland increases the excretion of the adrenocorticotropic hormone (ACTH). The cortisol deficiency compensation mechanism results in an increased production of adrenal gland androgens due to increased ACTH concen-

trations. There are two main forms of the disease due to 21-hydroxylase deficiency: classic salt-wasting or non-salt wasting form (with co-existing mineralcorticoid deficiency) and non-classic mild or late-onset and latent form [2].

The classic form of CAH manifests itself after birth through water and electrolyte disorders (such as dehydration, hyponatremia, hyperkalemia, hypochloremia) and acid-base balance disorders (metabolic acidosis), vomiting, diarrhoea, hypertension (25% of cases) as well as masculinization of external genitalia (in girls) due to androgen overproduction during fetal life. In boys scrotum skin discoloration may be observed as an effect of increased ACTH concentrations [1, 10]. In childhood CAH is associated with accelerated growth (100% of cases) and obesity due to fast body weight increase (95% of cases).

Later, in girls, hirsutism and acne are observed [1, 10]. Precocious pubic and axillar hair is another symptom. In cases of non-salt-wasting adrenal hyperplasia girls present with masculinization of genitalia and rapid physical development. The degree of masculinization in girls may vary, from slight clitoral hyperplasia to full masculinization – Prader stage 5. Additionally an absence of menarche and growing virilization, with lowered voice timbre and change of body silhouette may occur.

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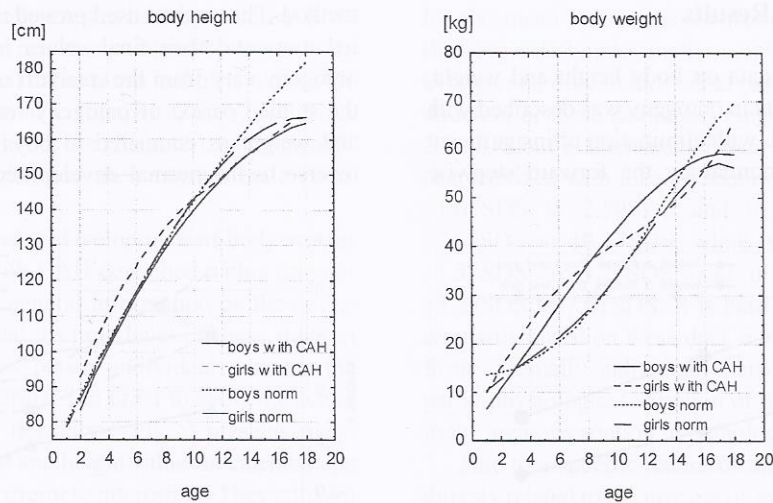


Fig. 1. Body height and weight development in children with CAH against the norm, described with a fifth degree polynomial.

In boys excessive androgen production has a significant effect on genital morphology, resulting in an enlarged penis. Accelerated growth in early childhood, precocious pubic and axillar hair, hirsutism and acne, lowered voice timbre and excessive growth of the muscular tissue [1] are also observed in males.

Children with congenital adrenal hyperplasia, when untreated or treated improperly (with insufficient dose of medication) are characterized by an advanced bone age due to androgen overproduction [11-13]. Initially children with this disorder are taller than their peers, however due to premature epiphyseal fusion of the long bones they reach lower final body height than normal children [12-15].

Studies of growth in children with neurohormonal system disorders indicate that its not the type of the etiological factor (a significantly elevated level of adrenal cortex hormones in CAH), but first of all its intensity and duration that have an effect on the process of their growth and on the values of their body height and weight. The stimulus interfering with normal growth should be eliminated as fast as possible, as the degree of disorders in the normal development of morphological features depends to a large extent on

the time and duration of its occurrence. Results of research on the relation between the time the CAH endocrinopathy is diagnosed and onset of replacement therapy with glucocorticosteroids (hydrocortisone) and mineralocorticosteroids (fludrocortisone acetate), and the final body height and sexual maturity are ambiguous and discrepant [11, 12, 15-28].

In this study the authors attempted to assess the degree and direction of deviations in two physical development traits: body weight and height in children with CAH as compared to the adopted reference system [29], and to individually assess bodily responses reflecting individual variation in growth and showing different direction and intensity of changes in time.

Material and Methods

In the study the authors used the material from a longitudinal study by Endocrinology Outpatient Clinic at the Karol Jonscher Teaching Hospital of Poznań University of Medical Sciences. The study sample included 13 boys aged from 0.4 to 19.6 years and 6 girls aged from 0.6 to 17.8 years, examined between 1989 and 2004. Periods of individual patient observation ranged from 2 to 16 years. Depending on the form of disease (classic salt-wasting or non-salt wasting, non-classic) treatment consisted in replacement therapy with the use of glucocorticoids (hydrocortisone dose of 10-25 mg/m² per day) and mineralocorticoids (fludrocortisone acetate dose of 0.05-0.1 mg per day).

In the study we used statistical procedures from CSS STATISTICA 7.0 software. Mean values of phenotypic traits of body weight and height and their standardized values were calculated. A polynomial function was used to assess the level of the analyzed traits in children with CAH. The degree and direction of deviations of the studied features in children with CAH were analyzed with the data standardization method and the calculated values were presented as SDS (standard deviation scores), while the growth trend was assessed with the straight-line regression model.

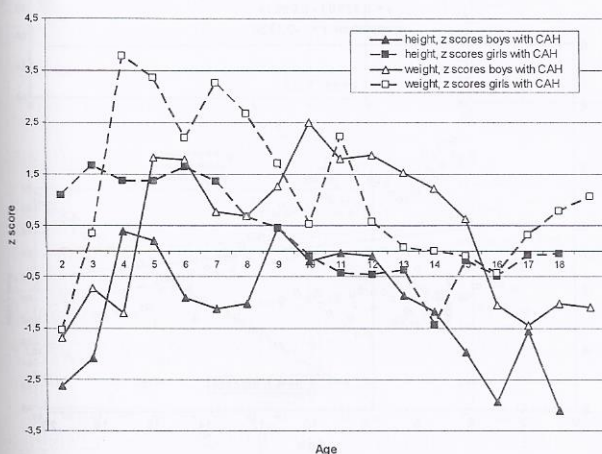


Fig. 2. Mean standardized values of body height and weight in children with CAH against the adopted reference system.

Results

Based on individual data on body height and weight, development of these traits in ontogeny was described with a fifth degree polynomial, with elimination of insignificant coefficients of the polynomial by the forward stepwise

method. The method used proved that the level of the studied traits and their final values in the studied period of ontogeny vary from the standard used. Girls with CAH in the studied period of ontogeny reach greater body height and weight as compared to boys with CAH. This is in reverse to the normal development of these traits in the

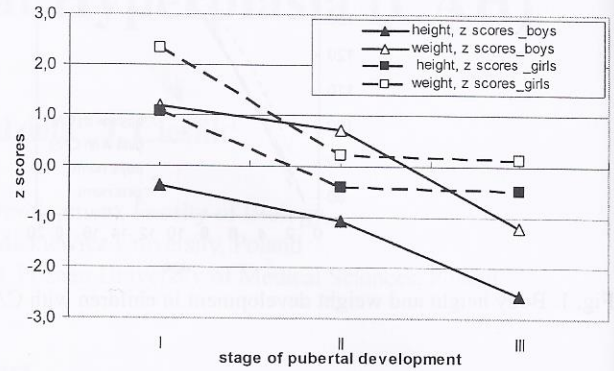
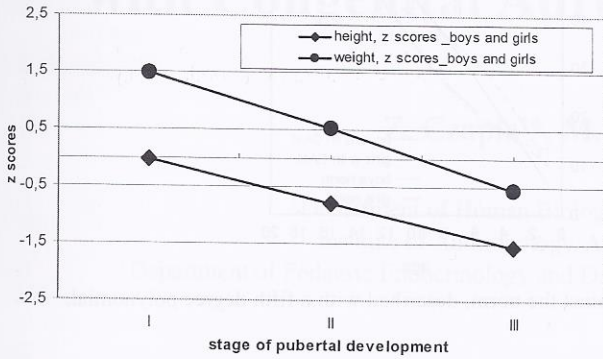


Fig. 3. Mean standardized values of body height and weight in children with CAH (jointly for both sexes) against the adopted reference system in distinguished stages of sexual maturation (I – prepubertal stage, II – pubertal stage, III – postpubertal stage), average z scores are statistically significant at $p < 0.01$

Fig. 4. Mean standardized values of body height and weight in children with CAH (separately for each sex) against the adopted reference system in the distinguished stages of sexual maturation (I – prepubertal stage, II – pubertal stage, III – postpubertal stage), average z scores are statistically significant at $p < 0.01$ for LSD test.

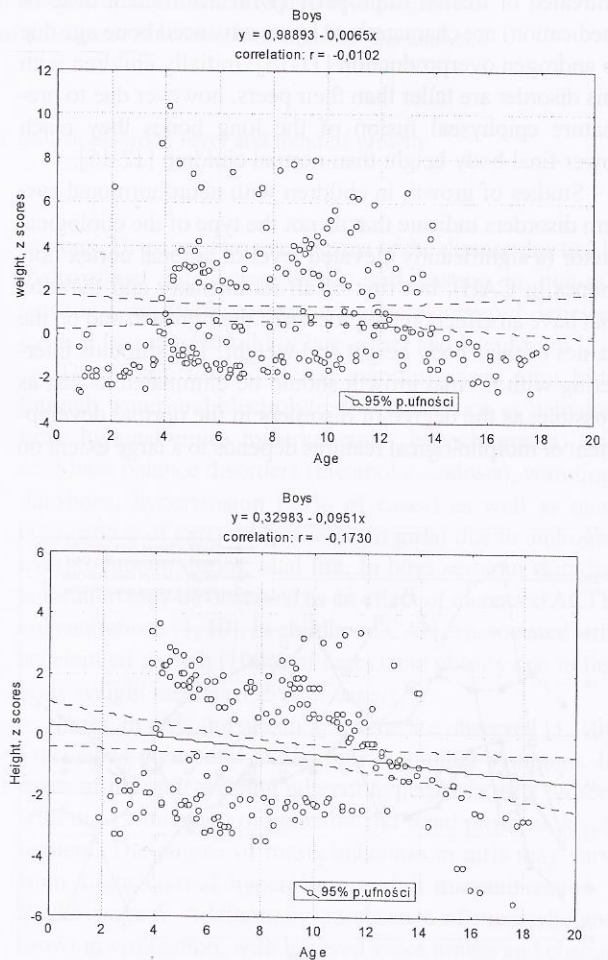
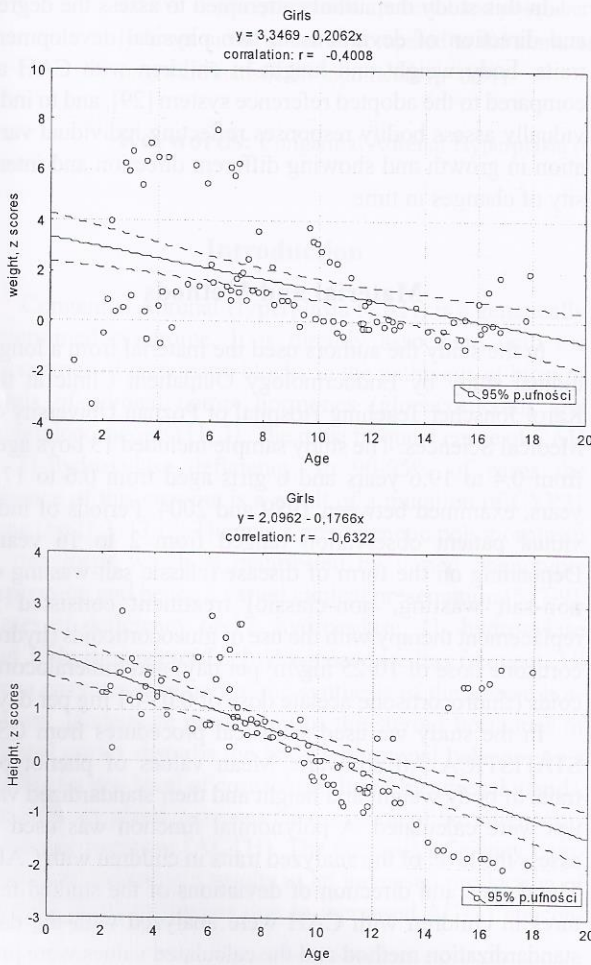


Fig. 5. The straight line regression of standardized body height and weight for all boys and girls with CAH against age (trend of growth).

course of ontogeny for both sexes in healthy children. Both boys and girls with CAH are characterized by lower body height values as compared to the norm and girls with CAH have greater body weight as compared to the norm. Boys with CAH, on the other hand, are characterized by significantly lower body weight than their normal male peers (Fig. 1).

The above given level of development of body weight and height in children with CAH described with a polynomial provides only very general information on the deviations from a physiological average level of these traits in normal children. For this reason individual data for the studied traits were standardized in order to show the actual degree and direction of deviations. Fig. 2 presents mean standardized body weight and height values in calendar age groups. The results are extremely interesting. They confirm the existence of pathological interindividual variation, reflecting differences in bodily reactions, an in degree and direction of deviations in the studied children with CAH as compared to the norm. In the studied period of ontogeny body height of boys described with standardized means deviates from the norm by values ranging from -3.10SDS to 0.45SDS and in individual cases by values from -5.49SDS to 3.69SDS . In girls the scale of these deviations

for the mean values ranges from -1.42SDS to 1.66SDS showing a definitely smaller amplitude of oscillations than in boys, and only in individual cases in girls the degree and direction of these deviations ranges between -2.00SDS to 2.85SDS but is also smaller than in boys. Body weight is characterized with mean deviations for boys ranging from -1.67SDS to 2.50SDS and in individual cases from -2.62SDS to 10.37SDS , while in girls on average from -1.52SDS to 3.77SDS , and in individual cases from -3.25SDS to 7.61SDS . It is hard to indicate any trend or regularity based on these data, but the analysis clearly confirms unusually individual character of the deviations in partly physiological variation of these traits but most of all in the area of variation in pathological deviations.

Due to a specific nature of the studied endocrinopathy directly related to the process of growth of physical traits as well as to the development and maturation of the sexual system the studied material was subdivided into groups according to the criterion of maturity of secondary sex characters, proposed by Tanner [30-32]. Three following stages were distinguished on the basis of the average age of occurrence of sexual maturation symptoms: prepubertal stage, grouping boys under the age of 12.5 years and girls under the age of 10.5 years, pubertal stage, grouping boys aged

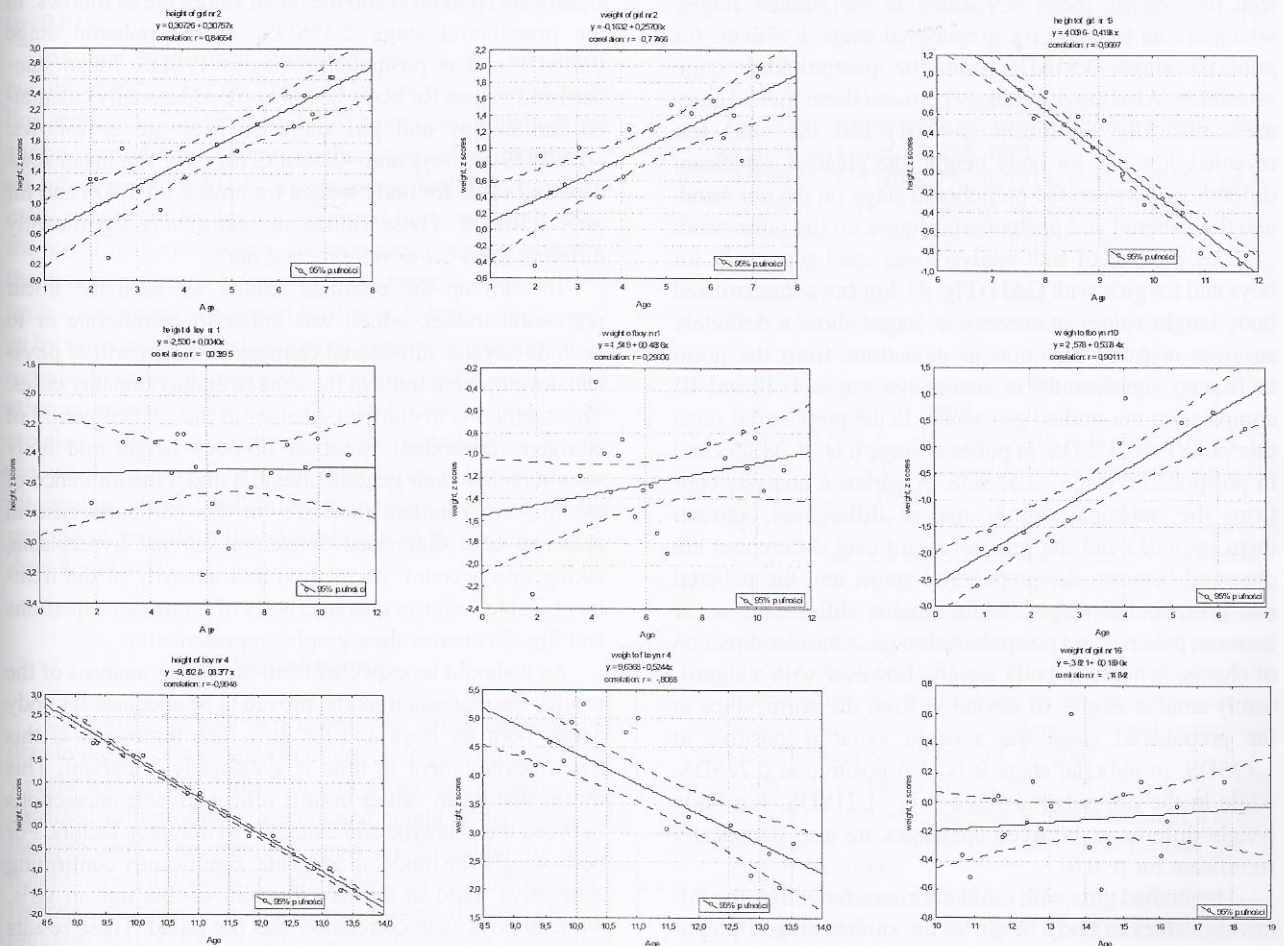


Fig. 6. Selected examples of straight line regression of standardized body height and weight for individual cases of children with CAH (trend of growth).

from 12.5 to 15 years and girls aged from 10.5 to 13 years, and postpubertal stage grouping boys over 15 years of age and girls over 13 years of age. A degree and direction of deviations in body weight and height were assessed in these three distinguished stages of ontogeny.

The results obtained for individual stages enable a more accurate assessment of the degree and direction of disorders occurring during the growth of the analyzed traits. Figure 3 shows mean deviations of body weight and height based on standardized values, regardless of the sex in the studied group of children with CAH. The deviations in body weight and height in the three distinguished stages are characterized by a clear direction, and in successive stages similar differences in deviations between the studied traits are retained, ranging from 1.00SDS to 1.50SDS.

The presented results reflect adverse changes in the growth of the traits under study. Namely: body height (average) in successive stages (I, II, III) shows a progressively negative degree of deviation, from -0.02 SDS in the prepubertal stage through -0.80 SDS in the pubertal stage to -1.56 SDS in the postpubertal stage. What is most important, the variance analysis showed that the values differed statistically significantly ($p < 0.01$) between one another and an additional analysis with the LSD test, revealed the greatest significant difference between the prepubertal stage, and pubertal and postpubertal stages. Body weight is characterized by average mean deviations in the studied stages, which are as follows: for prepubertal stage 1.47SDS, for pubertal stage 0.51SDS and for postpubertal stage -0.55 SDS. Also the differences between these mean values are statistically significant ($p < 0.01$) and the LSD test revealed, just like for body height, the greatest significant differences between the prepubertal stage on the one hand, and the pubertal and postpubertal stages on the other hand.

This method of trait analysis was used separately for boys and for girls with CAH (Fig. 4). For boys standardized body height values in successive stages show a definitely stronger negative direction in deviations from the norm increasing significantly in successive stages I, II and III compared to the studied girl group. In the prepubertal stage this value is -0.37 SDS, in pubertal stage it is -1.08 SDS and in postpubertal stage -2.55 SDS. A variance analysis confirms the statistical significance of differences between them ($p < 0.01$) and the greatest significant differences are observed between the prepubertal stage, and the pubertal and postpubertal stages, while smaller differences occur between pubertal and postpubertal stage. A similar direction of change is noted in body weight, however with a significantly smaller degree of deviation from the norm, since in the prepubertal stage the average value is positive at 1.19SDS, in pubertal stage it is also positive at 0.72SDS, while in the postpubertal stage it is -1.21 SDS. For body weight differences between the stages are also statistically significant for $p < 0.01$.

The studied girls with CAH are characterized by the following values of body height in the studied stages: prepubertal stage 1.07SDS, pubertal stage -0.40 SDS and postpubertal stage -0.46 SDS. These deviations from the norm are considerably smaller compared to boys. Differences

Table 1. Characteristics of the parameters of equations of straight line regression for all children with CAH, regression of the standardized body height and weight against age.

Sex and traits	B_0	p for B_0	R^2	B_1	r	p for R^2, B_0, r
Boys B-v	0,008	0,977	0,03	-0,079	-0,176	0,009
Girls B-v	2,096	0,000	0,399	-0,176	-0,632	0,000
Boys weight	0,986	0,011	0,000	-0,006	-0,010	-0,876
Girls weight	3,346	0,000	0,161	-0,206	-0,401	0,000

between the individual stages are also statistically significant, which also indicates adverse changes in the growth process ($p < 0.01$). The LSD test revealed the greatest significant differences between stage I and stage II and between stage I and stage III.

A similar direction of change in time was observed for body weight of girls, although in this case the direction of change is positive in relation to the reference system. The noted differences between the stages are also statistically significant ($p < 0.001$) and the mean values are as follows: in the prepubertal stage 2.33SDS, in the pubertal stage 0.21SDS and in postpubertal stage 0.12SDS. Mean standardized values for body height were additionally calculated for all boy and girl subjects. They are as follows: -0.67 SDS for boys and -0.46 SDS for girls. The mean standardized value for body weight for boys is 0.93SDS and for girls 1.50SDS. These values are statistically significantly different from the developmental norm.

To sum up the obtained results we used the linear regression model, which was either to corroborate or to exclude adverse directional changes in the growth of physical development traits in the studied endocrinopathy cases. This method is to confirm whether in the studied period of ontogeny dependent variables of body height and body weight realize their genetic potential under the influence of external environment factors, in this particular case in presence of a diagnosed congenital adrenal hyperplasia, taking into account the method and intensity of the treatment. Table 1 shows characteristics of regression equations and Fig. 7 contains their graphic representation.

As it should be expected from the earlier analysis of the results, the regression model proved to be adequate for body height both for boys and for girls. The regression of this trait's development in time is statistically important. This means that mean values in time reflect adverse interactions between the genotype and external environment factors. For body weight the model is adequate, significantly confirming a negative trend in the development of this trait in girls, while in boys such correlation was not found. These results are very interesting but unfortunately reflect adverse changes in the described subject group of children with CAH. This picture is also only a description of a general

trend in the development of the investigated traits in time in the studied subject group. For this reason individual regression lines were calculated for the traits to confirm, from another point of view, interindividual variation in responses to the studied factor. The results obtained for multidirectional development trends for selected patients are shown in Fig. 8.

Discussion

The obtained results permit to conclude that the process of growth of body height and weight in children with CAH is significantly different from the average standard for normal children. This has been corroborated by earlier publications [10-15, 20, 22, 33]. The significant outcome obtained in our study is related to the assessment of growth of the analyzed physical development traits in the three distinguished stages of ontogeny, i.e. in prepubertal, pubertal and postpubertal stage. This procedure permits to assess the level of development of these traits and the direction of their deviation from the reference system – norm used. The results clearly indicate that both body height and weight, regardless of the sex, in successive stages of ontogenetic development have progressively lower values as compared to the norm and that the differences between the values in the analyzed stages are statistically significant ($p < 0.01$).

Another significant cognitive aspect of this study encompasses the results obtained by the use of the straight line regression model. Both body height and weight in the studied period of ontogeny are characterized on average for all subjects with CAH by a negative growth trend, statistically significant for body height and body weight (except for boys). This means that, for the studied endocrinopathy, the genetic potential responsible for determination of these traits in ontogeny is affected by this endocrinopathy as well as by other unidentified factors of external environment. In individual cases the regression method used revealed variation in growth trends for the studied traits in time, which are also statistically significant but differ from the norm for the whole group of children with CAH. This is another interesting result confirming individual variation of the process of growth of the studied traits in the group of children with CAH.

Conclusions

Congenital adrenal hyperplasia can cause major disorders in the process of growth of the biological traits of body weight and height. A decline was observed in mean standardized values of body weight and height in the course of development. The changes apply in particular to body height. Great individual diversity and variation of trends in realizing the genetic potential was observed in the studied children with CAH, which was confirmed by individual straight line regression lines. The obtained results confirm individual variation in responses to the administered

hormonal treatment, depending on the time of commencement and on duration of therapy but most of all on patients' individual susceptibility to treatment, which has been confirmed by the literature on the subject literature on the subject [12-15, 23-28, 33, 34]. Despite early diagnosis of the endocrinopathy and despite administered therapy, the physical development of the studied children is significantly disturbed.

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