

Complex Treatment of Children Affected by Undifferentiated Connective Tissue Dysplasia Combined with Bone Mineral Density Reduction

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Abstract

Introduction: Undifferentiated connective tissue dysplasia has a number of common mechanisms with inadequate bone formation, including lack of its mineralization in childhood. The frequency of combinations of connective tissue dysplasia with osteopenia and osteoporosis is quite high, which leads to the hypothesis of the advisability of complex treatment of such combinations. The purpose of the research is to develop and evaluate the clinical effectiveness of the integrated treatment of connective tissue dysplasia and osteopenic syndrome in children. **Materials and Methods:** We examined 160 children aged 3–16 years, divided into 2 groups that were identical in number and age and sex content. Undifferentiated connective tissue dysplasia and reduced bone mineral density (BMD) were diagnosed in all children included in the study. The concentration of 25-hydroxyvitamin D, calcium, and magnesium in the blood and excretion of glycosaminoglycans (GAGs) were determined. Ultrasonic densitometry of the calcaneus was performed. Patients were under prospective observation for 2 years. In the comparison group, calcium and Vitamin D3 preparations were administered in the age-related therapeutic dosage during 6 months, followed by a change to prophylactic doses. In the main group, in addition to Vitamin D3 and calcium, a preparation of sodium chondroitin sulfate was given within 3 months, and after a break of 6 months, a 3-month course was repeated, as well as a magnesium preparation in the age-related therapeutic dosage, the duration of the course was 6 months, with a change to a prophylactic dose until the end of observation. **Research Findings:** The *t*-test level for densitometry in the main group increased more rapidly than in the comparison group. The significance of differences with the control group was absent after 18 and 24 months of treatment. After 24 months, significant differences in favor of the main group were determined by the rate of normalization of the BMD level ($\chi^2 = 11.90$, $P = 0.015$). At the same time, there were no significant differences in the content of the metabolite of Vitamin D and calcium in the blood. In contrast, magnesium content after 6 months revealed significant differences between groups of children with pathology in favor of the main group, which persisted until the end of the study. The decrease in GAG excretion in the study dynamics was revealed only in the children of the main group. This process continued after 6 months and at least up to 9 months, and during the entire observation period from 6 to 24 months, this indicator was lower in the main group than in the comparison group. **Conclusions:** (1) The use of complex treatment of children affected by undifferentiated connective tissue dysplasia in combination with BMD reduction helps to increase BMD and in a significant number of cases (over 20%) contributes to full normalization of BMD within 2 years. (2) Complex treatment also provides correction of pathogenetic mechanisms of connective tissue disease, which should have a positive effect on the state of connective tissue and its adequate formation in the case of timely administration of therapy.

Key words: Bone mineral density, calcium, complex treatment, glycosaminoglycans, magnesium, undifferentiated connective tissue dysplasia, vitamin D

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Received: 22-12-2017

Revised: 27-12-2017

Accepted: 31-12-2017

INTRODUCTION

Connective tissue development is controlled by a complex of genes encoding proteins and enzyme complexes which compose it and make a synthesis of non-protein components.^[1,2] Connective tissue formation disorders are usually associated with the emergence of undifferentiated dysplasia syndrome and only in a relatively small number of cases with dysplasia present in specific genetic syndromes (Marfan, Ehlers-Danlos, Stickler syndromes, etc.).^[3,4]

Currently, the incidence of connective tissue disease (CTD) in the population is increasing,^[5-7] which may be due to both the impact of adverse environmental factors, and in part, to better detection and accountability of this pathology.

The formation of connective and bone tissue is conjugate, which is associated both with the generality of origin and with the impact of unified pathogenetic mechanisms.^[8,9] Therefore, it is possible that the frequency of bone tissue formation disorders in children with connective dysplasia will be higher, and the clinical course is more severe. This hypothesis is considered and proved in a number of recent researches.^[10,11]

Treatment of children with CTD involves a number of drugs, usually not used in the complex of prevention and treatment of bone mineral density (BMD) reduction within the same period, whereas it is advisable to use a combination of both approaches in the case of a coexisting pathology.

The purpose of the research is to develop and evaluate the clinical effectiveness of the integrated treatment of connective tissue dysplasia and osteopenic syndrome in children.

MATERIALS AND METHODS

We examined 160 children aged 3–16 years (the average age of 10.6 ± 1.1 years), including 62 boys and 98 girls.

Inclusion criteria

The following criteria were included in the study:

- Age from 3 to 16 years;
- Presence of phenotypic signs of undifferentiated CTD (not <4), allowing to determine this diagnosis;

- Presence of BMD reduction in at least 25 percentile of the age norm;
- Full survey according to the study protocol;
- Passage of the full course of the developed therapy and further prospective observation for at least 6 months.

Exclusion criteria

The following criteria were excluded from the study:

- Presence or anamnesis of concomitant severe somatic, oncological, chronic infectious diseases suggesting the likelihood of development of secondary osteoporosis or other bone tissue damages as a result of exposure to this pathology and/or its treatment;
- Presence of diagnosed pathological genetic syndromes, including differentiated forms of CTD;
- Reasonable doubt in the conduct of recommended treatment in outpatient settings.

Inclusion of children in the study was carried out with the informed consent of themselves (aged 14 and older) and/or their parents (foster parents).

Connective tissue dysplasia was determined in accordance with the Russian recommendations "Hereditary Disorders of Connective Tissue Structure and Functions."^[12]

The content of the main circulating active Vitamin D metabolite - 25-hydroxyvitamin D (25(OH)D),^[13] calcium, and phosphorus in serum and BMD was determined in the examined group.

The concentration of calcium was studied by a unified colorimetric method (with o-cresolphthalein-complexon) and phosphorus by a molybdate UV method. The content of 25(OH)D was determined using an enzyme-linked immunosorbent assay with the use of the test systems of ZAO Bio HimMak. Vitamin D deficiency was diagnosed at a concentration of 0–20 ng/ml, Vitamin D deficiency of 21–29 ng/ml, and the optimal assurance level was considered at vitamin concentration of 30–75 ng/ml.^[14]

Calcaneus densitometry was performed on the sunlight 2000 apparatus.

Correction of bone tissue formation disorders was carried out depending on the group. In the comparison group (80 people,

32 boys and 48 girls, the average age of 10.7 ± 1.0 years), calcium D3 Nycomed was prescribed in age-related treatment doses for 6 months, followed by a transition to preventive doses. In addition, multivitamin preparations were used, and a diet with mandatory introduction of products containing calcium was prescribed.

In the main group (80 people, 30 boys and 50 girls, the average age of 10.5 ± 1.1 years), in addition to using Vitamin D and calcium D3 Nikomed in the same dosage as in the comparison group, additional drug correction methods for CTD were used. Sodium chondroitin sulfate was prescribed for 3 months with a repeated 3-month course after a break of 6 months. A magnesium preparation was used in the age-related treatment doses, the course duration was 6 months, with the transition to the maintenance dose until the end of the research.

The control group consisted of 50 practically healthy children (BMD within 10% of age standards, no more than 2 phenotypic signs of CTD) at the age of 4–15 years (the average age of 10.9 ± 0.9 years). During the initial examination, this group was recommended a rational calcium content diet or intake of calcium preparations in preventive doses.

Statistical analysis of the results was carried out using SPSS version 20 for Windows.

The data processing system included automated quality control of information preparation (exclusion of results not related to the data series according to Romanovsky criterion) and grouping of data according to specified criteria. Analysis of continuous variables was carried out using parametric methods (student), or, if the applicability criteria (the variance equality and the normality of sampling distribution) were not met - by non-parametric methods (Mann–Whitney, Wilcoxon). To analyze the conjugacy tables, we used the two-sided Fisher's exact test and χ^2 criterion.

When carrying out the statistical analysis, the critical significance level of p and α was assumed to be 0.05.

RESEARCH FINDINGS AND DISCUSSION

The results of a comparative analysis of BMD level in the examined groups are presented in Figure 1.

In the control group of practically healthy children, BMD indices practically did not change during the period of prospective observation (taking into account the calculation of the criterion according to age) and were within the normal.

In the comparison group, the use of the treatment program ensured an increase in the t -test during the 1st year of the research by 8.6% from the baseline ($P > 0.05$) and within 2nd year by 14.3% ($P > 0.05$). Despite the absence of significance of differences with the initial indices, the

achieved result provided a reduction of differences with the control group - from 25.5% at the primary examination ($P = 0.01$) to 13.9% at 24 months ($P > 0.05$).

The t -test level in the main group increased more rapidly than in the comparison group. After 12 months, the excess of the average index over the one determined at the beginning of the study was 14.1% ($P > 0.05$), and after 24 months, it reached 22.5% ($P = 0.037$). The significance of differences with the control group was absent after 18 and 24 months of treatment. At the same time, there were no significant differences in the indicator between the examined groups of children suffered from BMD reduction combined with undifferentiated CTD with different treatment modes.

Table 1 presents the distribution of children in groups, depending on the degree of BMD reduction according to the survey terms.

In the period of 12 months, there were no significant differences between groups in the number of individual categories allocated depending on BMD reduction. After 24 months, significant differences were determined in favor of the main group ($\chi^2 = 11.90$, $P = 0.015$).

Figure 2 shows data on the dynamics of the content of 25(OH)D, a Vitamin D metabolite, in children's blood for the groups examined.

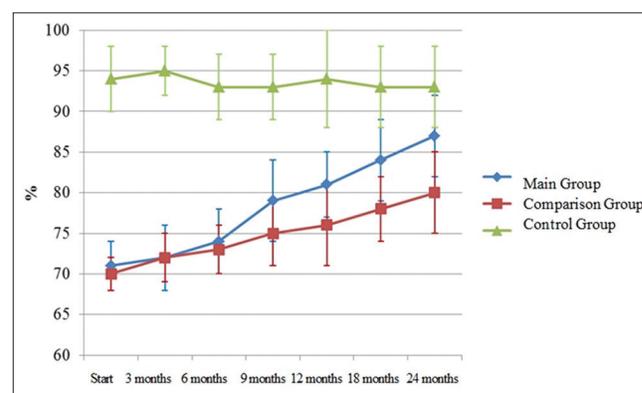


Figure 1: Comparative analysis of bone mineral density level

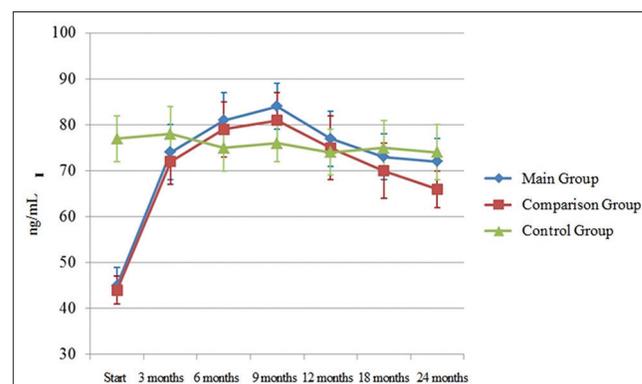


Figure 2: Data on the dynamics of the content of 25(OH)D, in children's blood for the groups examined

The growth of this indicator in the groups of children receiving treatment was observed quite quickly and thanks to the use of therapeutic doses of drugs, and its level exceeded the parameters of the control group during the 1st year of the research. There were no significant differences between the groups depending on the therapy, as well as with the control group from the time of the first reexamination (3 months) and until the end of the observation.

Figure 3 shows the dynamics of calcium content in the blood of the children examined.

The calcium content in the blood behaved similarly to those of Vitamin D metabolite. Significant differences with the control index were leveled after 3 months, within the periods of 6 and 9 months intervals, there was an excess over the control group level, and starting from 12 months, the values of the indicator were leveled in all three groups of the examined children.

Figure 4 shows the data on the magnesium content in the blood of the children examined.

Throughout the study, the magnesium content in the blood of the children of the main group exceeded the indices of both subgroups of children with CTD in combination with osteopenic syndrome and had no significant variations.

The treatment carried out had a definite effect on this indicator only in the main group. Within 3 months, significant differences with the control group were not determined. After 6 months, significant differences were found between groups of children with pathology (by 15.7%, $P = 0.033$), remaining until the end of the study.

Glycosaminoglycans (GAGs) renal excretion dynamics for the groups compared is shown in Figure 5.

The decrease in GAG excretion during the study was revealed only for the children of the main group. This process continued after 6 months and at least up to 9 months, with differences in the baseline at 60.9% ($P < 0.001$) and 59.1% ($P < 0.001$). Nevertheless, there was a significant increase in the level of the indicator over the control throughout the study. This indicates the preservation of pathogenetic mechanisms of CTD in the active state.

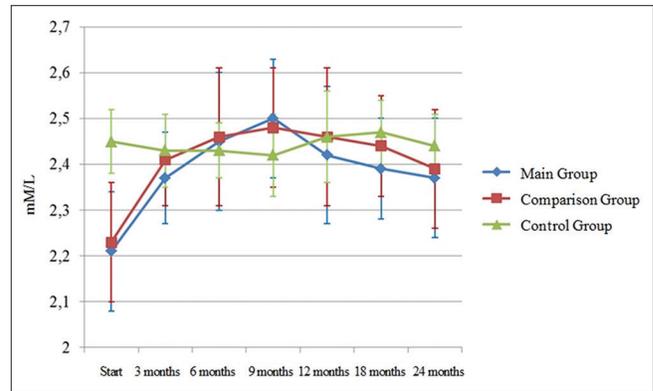


Figure 3: Dynamics of calcium content in the blood of the children examined

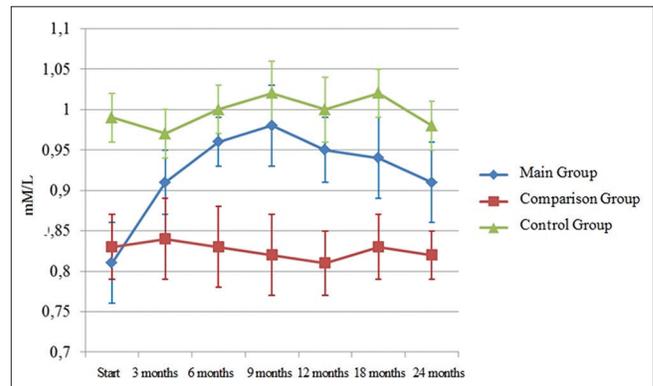


Figure 4: Dynamics of the magnesium content in the blood of the examined children

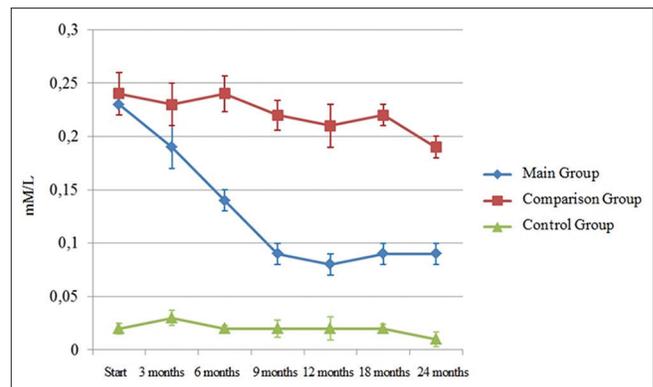


Figure 5: GAG renal excretion for the examined children

Table 1: Distribution of children by the degree of BMD reduction

Group	Examination period								
	Start of research			12 months			24 months		
	>25%	10-25%	<10%	>25%	10-25%	<10%	>25%	10-25%	<10%
Main									
Absent (%)	80 (100)	-	-	37 (46.2)	41 (51.3)	2 (2.5)	14 (17.5)	49 (61.3)	17 (21.2)
Comparison									
Absent (%)	80 (100)	-	-	49 (61.3)	31 (38.7)	-	34 (42.5)	41 (51.3)	5 (6.2)

BMD: Bone mineral density

Closing

Studies of various authors, confirmed by our data, revealed an increase in the frequency of osteopenic syndrome in children with undifferentiated connective tissue dysplasia.^[15]

Proceeding from the hypothesis of the combined genesis of these disorders, we conducted the study of the complex treatment effectiveness, including measures to correct mineral metabolism (calcium and magnesium simultaneously) disorders, as well as a set of additional treatment modes.

A normalizing effect of the applied therapy on the complex of pathogenetic mechanisms of both diseases was revealed. An increase in the calcium content in the blood and its assimilation into bone tissue was determined. Prospective data obtained during a 2-year survey indicate a significant increase in BMD, exceeding the rate of increase in the control group. After 2 years, there was a significant increase in both the average BMD and the number of children with a practical normalization of this indicator.

At the same time, there was a gradual normalization of the mechanisms associated with the CTD. In particular, a decrease in GAG excretion, significant in relation to the baseline and comparison group, was achieved. These changes may, according to a number of researchers, reflect an improvement in the conditions for the formation of connective tissue,^[16,17] and accordingly, contribute to a decrease in the severity of morphologic and functional disorders during the life to come.

CONCLUSIONS

1. The use of complex treatment of children affected by undifferentiated connective tissue dysplasia in combination with BMD reduction helps to increase BMD and in a significant number of cases (over 20%) contributes to full normalization of BMD within 2 years.
2. Complex treatment also provides correction of pathogenetic mechanisms of CTD, which should have a positive effect on the state of connective tissue and its adequate formation in the case of timely administration of therapy.

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Source of Support: Nil. **Conflict of Interest:** None declared.