International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 02, 2020
ISSN: 1475-7192

Occurrence of Clinical Options of Undifferentiated Connective Tissue Dysplasia in Uzbek Population

[1]Shodikulova Gulandon Zikrievna, [2]Babamuradova Zarrina Bakhtiyarovna

Absrtact--

Object: *To study the occurrence of clinical variants of undifferentiated connective tissue dysplasia (NDST) in the Uzbek population.*

Methods: *105 individuals were examined, including 49 (46.4%) males and 56 (53.6%) females aged 15 to 28 (20.13 ± 0.66) years with signs of NDCT.*

Findings: *The incidence of NDCT in women is within 40%, in males 66.0%. An analysis of the distribution of NDST by place of residence showed a slight predominance of city residents (60 patients lived in the city, 45 in the countryside), an increase in the frequency of HLA gene class II was observed: HLA DRB1 *, DQA1 * 04: 01 and DQB1 * 04: 01/2 . The incidence of clinical options is joint hypermobility (100%), changes in the shape of the spine (44%), chest (43.8%), skin extensibility of varying severity (38.8%), small developmental anomalies (21.1%) and flat feet (20.4%). The frequency of combinations of external hair dryers: a combination of 6 revealedat 5 (4,5%), 5-th – at 11 (10%), 4-th – at 21 (20%), 3-rd – at 26 (24,3%), 2-nd – at 31 (30,6%) examined*

Conclusions**:** *Thus, the early detection of signs of NDCT in young people among the Uzbek population will optimize early diagnosis and predict the outcome of the disease.*

Key words*--undifferentiated connective tissue dysplasia; clinical options; external and internal hair dryers; HLA system.*

I. INTRODUCTION

Connective tissue dysplasia (DST) is a hereditary disorder of the connective tissue of a multifactorial nature, combined into different syndromes and phenotypes by a commonality of external and visceral symptoms.

In our country, in order to improve the quality of medical care for the population over the years of independence, a health system transformation program has been implemented and large-scale use of the latest diagnostic methods has been introduced. Thus, effective medical care for children and adolescents ensured timely detection, early diagnosis, treatment and prevention of possible complications of undifferentiated connective tissue

[1]*Doctor of Medical Sciences, Associate Professor, Head of the Department of Internal Medicine No. 3 and Endocrinology,Samarkand State Medical Institute,140100, Samarkand,st. Amir Timur, 18. Email: shodikulovagulandom@mail.ru*
[2]*Basic doctoral student of the 3d course of the Department of Internal Medicine No. 3 and Endocrinology of Samarkand State Medical Institute 140100, Samarkand, st. Amir Timur, 18.Email:dr.zarrina.b.b@mail.ru*

DOI: 10.37200/IJPR/V24I2/PR200434
Received: 20 Dec 2019 | Revised: 05 Jan 2020 | Accepted: 18 Jan 2020

dysplasia. According to the Ministry of Health, the birth rate of children with congenital malformations decreased 1.3 times and child mortality 3.1 times.

In the world among young people, in order to increase the effectiveness of early diagnosis, treatment and prevention of possible complications of undifferentiated dysplasia of the connective tissue, numerous scientific studies have been carried out, including the rationale for the formation and course of dysplastic changes in adolescents and young adults; improvement of the early diagnosis system; assessment of the state of the HLA system, collagen formation; development of modern methods of treatment and prevention of possible complications in the light of modern requirements.

Materials and methods

Clinical studies were conducted for the period 2017-2019. on the basis of the Samarkand city medical association, the Samarkand regional teenage clinic and 1 - clinic of the Samarkand medical institute. The population survey included 105 individuals, including 49 (46.4%) male and56 (53,6%) females aged 15 to 28 (20,13±0,66) years with signs of NDCT. The distribution of patients with NDCT depending on age and gender is presented in the table 1.

Table 1. Distribution of MVP patients by age and gender.

Age	**Women**		**Men**		**Total**	
	abs.	%	abs.	%	abs.	%
Before 18	22	38,7	9	17,5***	37	28,8
19-22	21	37,8	32	66,0***	53	51,0
Over 22	13	23,4	8	16,5	21	19,7
Total	56	53,6	49	46,4	105	100,0

Note: * - differences regarding the data of a group of women are significant(*** - P<0,001)

II. LITERATURE REVIEW

According to classical ideas, DST is not a syndrome or disease, it is a pathological condition caused by a genetically impaired formation of connective tissue in the embryonic or postnatal periods.

Morphological changes in them determine the variety of clinical manifestations: from benign subclinical forms to multiple organ and polysystemic pathologies with a progressive course [2; p. 266-281, 4; p. 23-31, 9; p. 714, 13; p. 188] . According to the literature, its basis is collagen structure defects, which lead to a change in the fibrous structures and the main substance of the connective tissue, leading to a violation of the structure and function of tissues and organs. Together, they significantly reduce the quality of life of patients, affect the course of other pathologies, causing an unfavorable prognosis for patients [6; c.123-129, 14; c.131-135, 15; c.22-28].

DOI: 10.37200/IJPR/V24I2/PR200434
Received: 20 Dec 2019 | Revised: 05 Jan 2020 | Accepted: 18 Jan 2020

The leading role in the development of DST belongs to mutations of the genes responsible for the synthesis and formation of the spatial structure of collagen, as well as the formation of components of the intercellular matrix or enzyme genes that take part in fibrologenesis [8; p.5-9, 26; p.217-223 , 32; c. 271-278, 34; c. 1085-8, 35; c. 1134–1142]. Mutations of genes lead to the development of many disorders of the formation of connective tissue, the number of which today has more than 250 syndromes. Most of these syndromes are very rare. These include differentiated forms of DST: Marfan syndrome (SM) [30; p. 1431–1451], Ehlers-Danlo syndrome (EDMS), imperfect osteogenesis (BUT), and many others. The population frequency of monogenic connective tissue defects is not so great, its undifferentiated forms of connective tissue dysplasia are extremely common. According to V.I. Bugaeva (2010-2011), NDCTs can be caused by genetic changes, but also develop due to the effects of various adverse effects of environmental conditions [3; p. 266-281, 46; p. 590-595.]. In addition to severe, clinically significant forms of NDCT, there are also benign forms of dysplasia, in particular “benign joint hypermobility” [18; p. 15-17, 22; p. 19-23].

Due to the diversity of mutagenic effects, the ubiquitous presence of connective tissue, as well as the complexity of its structure and function, dysplastic changes can be either diffusely distributed (generalized) or local in nature [1; p. 121, 5; p. 40-44 , 11; p. 42-44, 16; p. 89-92, 47; p. 929–942]. In this regard, there is a variety of clinical manifestations of NDCT. They can be manifested by changes of a psychological nature, various autonomic dysfunctions, chronic fatigue syndrome, myopia and astigmatism, developmental anomalies of the kidneys and valvular apparatus of the heart and immune disorders [17; p. 15-20, 44; p. 275–284, 19; p. 48-51, 20; p. 25-30, 23; p. 13-19, 24; p. 84-89, 25; p. 61-67, 29; p. 140- 143.]. Often, practitioners who are not familiar with the variety of clinical manifestations of NDCT, due to the variety of clinical symptoms or syndromes, cannot see a single systemic defect in connective tissue. Therefore, in most cases, patients have to go to various narrow specialists for various clinical manifestations of NDCT. According to some reports, the frequency of detection of NDCT among young people reaches from 26 to 80%, among them 70% are women [10; p. 4-8, 228; p. 42-45, 42; p. 46-49.]. According to G.I. Nechaeva et al., From 74 to 85% of school-age children have various signs of DST [30; c. 1431-1451].

According to A.V. Klemenov, when using the main 6 or more external manifestations of NDCT, the frequency of detection of anomalies is no more than 20-25%.

Results

As can be seen from the presented material, the distribution of men and women was approximately the same, there was only a slight predominance of females. Basically, the disease was characteristic of the age group of 19-22 years (51.0%). However, an analysis of age-related morbidity by sex revealed some distinctive features. Thus, in female individuals, the incidence of NDST was the same in the age groups up to 18 years and 19-22 years (within 40%), while in males with a high frequency (66.0%) it was detected in the age group 19-22 of the year. Apparently, this was due to the different periods of transition of girls and boys from puberty and youth to a young age, as well as the maturity of the hormonal background. It should be said that in males during this period quite often there is a mismatch between growth and body weight, with the development of a deficiency of the latter.

DOI: 10.37200/IJPR/V24I2/PR200434
Received: 20 Dec 2019 | Revised: 05 Jan 2020 | Accepted: 18 Jan 2020

An analysis of the distribution of NDCT by place of residence showed a certain predominance of city residents (60 patients lived in the city, 45 in the village). At the same time, we have revealed the peculiarities of the incidence of NDST of males and females depending on the place of residence (Fig. 1). So, among residents of the city, the incidence was higher among females (35.7%), while in the villages, the incidence was higher among males (28.5%).

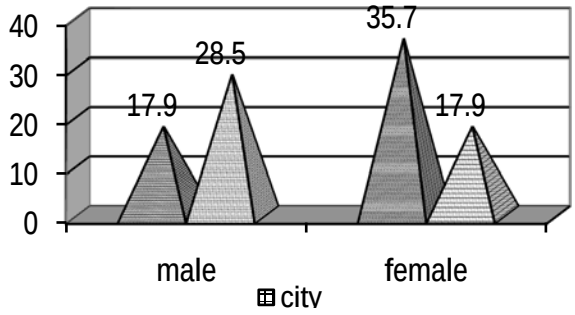

Figure 1. Distribution of patients with NDCT depending on location and gender.

As mentioned earlier, NDCT in studies was mainly characteristic of young people (Table 2).

Table 2. Sex, age and physiometric indicators in the examined groups of patients.

Signs	**M±m**		**Mmax-Mmin**
Age g	20,16±0,26		28,0-15,0
Girls	56	46,8	
Young men	49	53,2	
Weight kg	60,95±0,87		87-45
Height, cm	168,86±0,72		185-150
BMI	21,33±0,25		31,20-16,14

As can be seen from the above material, patients did not significantly differ in age. A study of sexual characteristics showed a predominance of girls (60.8%), but these differences were statistically insignificant. The differences we obtained may be due to ethnic and regional characteristics, as patients of Uzbek nationality predominated in our studies. The distribution of patients by place of residence showed approximately the same distribution, living both in the city and in the countryside.

Mass-growth indicators and BMI did not differ significantly in the studied groups of patients, while these were mainly normotrophics, in 11.3 and 10.9% of cases we revealed hypotrophics, in 6.2 and 7.3% of patients there was some excess weight body. According to the literature, NDST is characterized by an asthenic physique, while at

DOI: 10.37200/IJPR/V24I2/PR200434
Received: 20 Dec 2019 | Revised: 05 Jan 2020 | Accepted: 18 Jan 2020

the same time we did not reveal a pronounced asthenic physique, as normotrophics predominated and in 10-11% of cases of malnutrition. In some cases, the presence of excess body weight was also noted. In our opinion, such changes in weight and growth indicators are due to ethnic characteristics, as carbohydrate components predominated in the patients ’diet.

With NDCT, the main external manifestations are hypermobility of the joints of the upper and lower extremities; various changes in the spinal column in the form of scoliosis or kyphosis; chest deformity; pathology of the oral cavity, manifested by a high location of the palate, abnormal tooth growth and supernumerary teeth; flat feet and halluxvalgus, sandal-shaped slit; pronounced skin extensibility and vascular (venous) network on the skin and a tendency to form hematomas; eye pathology in the form of astigmatism and myopia; protruding ears with overgrown earlobes; asthenic physique, etc.

The study of probands showed a certain dependence of genetic factors in the formation of NDCT. It was found that among patients with NDCT, compared with the control group, a statistically significant increase in the frequency of the HLA class II gene was observed: HLA DRB1 *, DQA1 * 04: 01 and DQB1 * 04: 01/2. In patients, the frequency of occurrence of signs of NDCT in the 1st, 2nd and 3rd line of kinship was detected in 6 (8.5%), 9 (13%) and 5 (7%) of all the examined individuals. This suggests that the chance of developing complications is significantly higher in carriers of these alleles, which determines the predisposing role of these genes in the development of complications in the cardiovascular system. An analysis of the distribution of the frequency of occurrence of class II HLA genes depending on the variant course of the disease compared with the control group showed that, compared with the control group, the frequency of detection of genes HLA-DRB1*08 ($p<0,05$, OR=3,77, 95%CI=1,3-10,8) and DQA1*04:01 ($p<0,05$, OR=3,7, 95%CI=1,2-11,6) significantly higher in patients with scoliosis, HLA-DRB1*11 ($p<0,05$, OR=2,98, 95%CI=1,2-7,5) and DQA1*06:01 ($p<0,05$, OR=20,6, 95%CI=1,7-238,1), DQB1*04:01/2 ($p<0,05$, OR=5,42, 95%CI=1,7-17,4) with a combination of joint hypermobility with cardiac arrhythmias.

Given the above, it was of interest to study the external manifestations of NDCT. Analysis of the frequency of skeletal-skeletal external hair dryers in patients showed that spinal deformity was detected in 43 (44.3%)patients(Fig.2).

DOI: 10.37200/IJPR/V24I2/PR200434
Received: 20 Dec 2019 | Revised: 05 Jan 2020 | Accepted: 18 Jan 2020

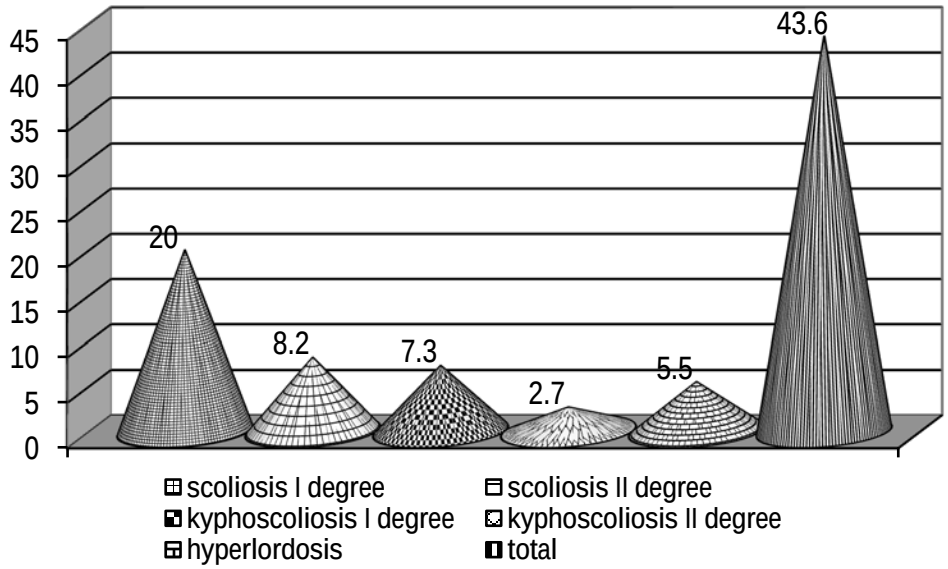

Figure 2. Frequency of various forms of spinal deformities in patients with NDCT.

The frequency of spinal deformity in 46 (43.6%) examined. Moreover, scoliosis of the 1st and 2nd degree was detected in 21 (20.0%) and 9 (8.2%) patients, kyphoscoliosis of the 1st and 2nd degree in 8 (7.3%)and 3 (2.7%) of the examined, hyperlordosis - in 6 (5.5%) patients. Analysis of the frequency of chestdeformities in patients showed their presence in 54 (51.5%) examined patients (Fig. 3).

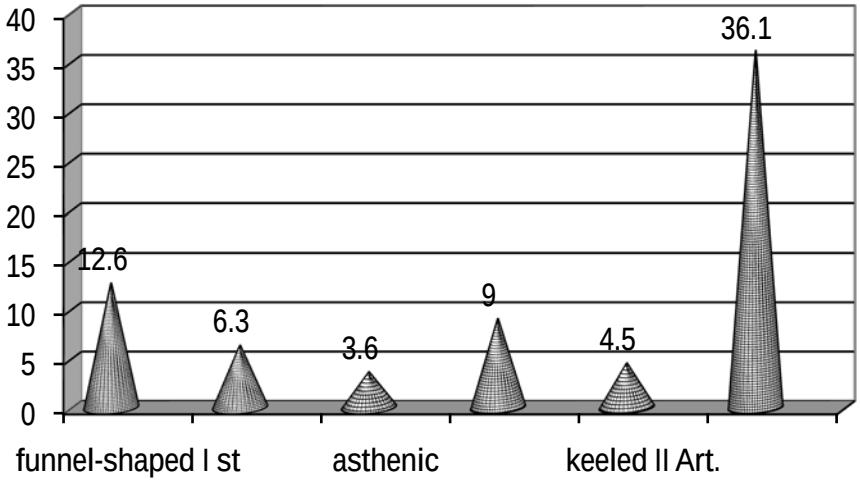

Figure 3. Frequency of various forms of chest deformities in patients with NDCT.

DOI: 10.37200/IJPR/V24I2/PR200434
Received: 20 Dec 2019 | Revised: 05 Jan 2020 | Accepted: 18 Jan 2020

Chest deformity was detected in 40 (36.1%) examined. They mainly manifested themselves as a funnel-shaped form of the 1st and 2nd degree in 14 (12.6%) and 7 (6.3%) patients, an asthenic form in 4 (3.6%), and a keeled form of the 1st and 2nd degree 10 (9%) and 5 (4.5%) of the examined. Skin manifestations of NDCT in the form of varying degrees of severity of skin distensibility were noted in 37 (38.1%) and 43(38.7%)patients (Fig. 4).

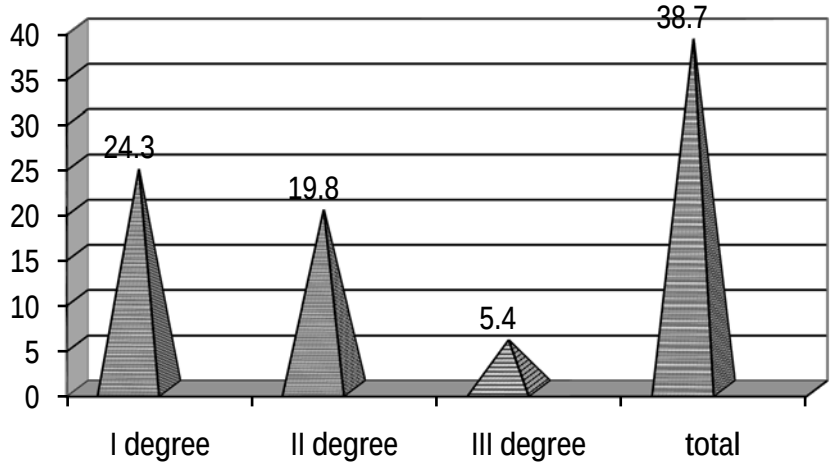

Figure 4. Frequency of skin extensibility of varying degrees in patients with NDCT.

Thus, in patients with NDCT, skin extensibility of the 1st, 2nd and 3rd degree was revealed in 27 (24.3%), 10 (19.8%) and 6 (5.4%) examined, respectively. Muscle hypotension was observed in 21 (21.6%) and 32 (28.8%) patients, respectively.

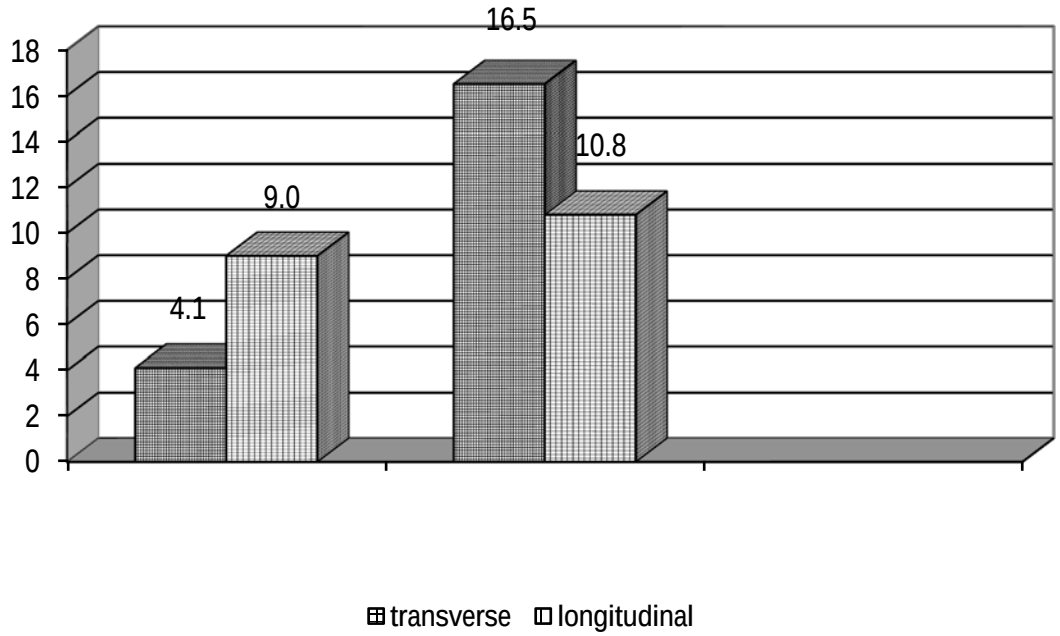

Figure 5. The incidence of flat feet in patients with NDCT

DOI: 10.37200/IJPR/V24I2/PR200434
Received: 20 Dec 2019 | Revised: 05 Jan 2020 | Accepted: 18 Jan 2020

Joint manifestations of NDCT are flat feet and hypermobility of the joints. Analysis of the frequency of flat feet showed their presence in 20 (20.6%) and 22 (19.8%) patients (Fig. 5). At the same time, transverse flatfoot was detected in 4 (4.1%) and 10 (9%) patients, longitudinal flatfoot - in 16 (16.5%) and 12 (10.8%) of the examined individuals.

Hypermobility of varying severity was detected in all examined patients (Fig. 6). So, in patients it was established in 44 (42.3%), 26 (25.2%), 23 (21.6%) and 12 (10.8%) examined. Small external developmental anomalies, which are manifested by large protruding ears and an enlarged earlobe, are another external hairdryer in patients with NDCT (Fig. 7). We identified these signs in 17 (16.2%) examined.

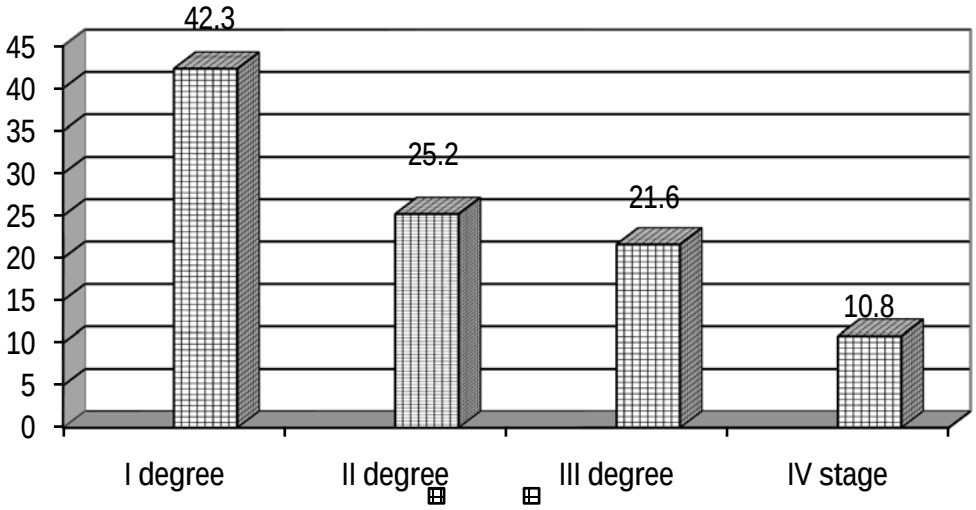

Fig. 6. The frequency of joint hypermobility of varying severity in patients with NDCT.

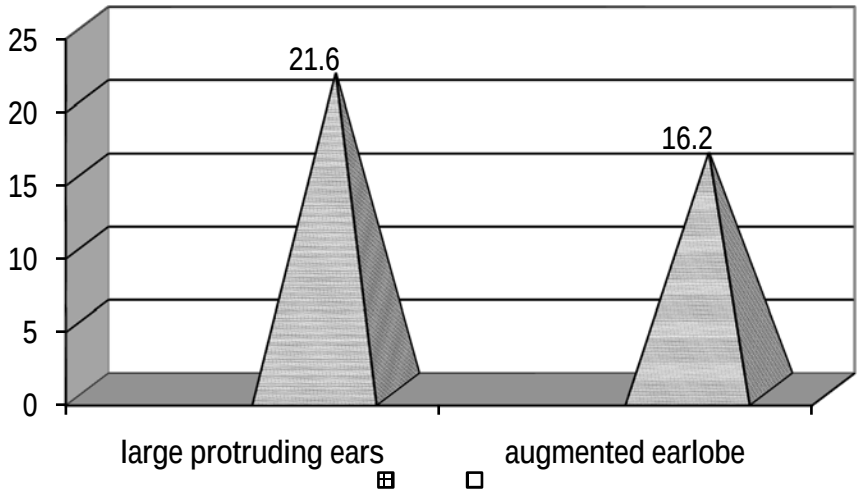

Figure 7. Frequency of small developmental abnormalities in patients with NDCT.

DOI: 10.37200/IJPR/V24I2/PR200434
Received: 20 Dec 2019 | Revised: 05 Jan 2020 | Accepted: 18 Jan 2020

As can be seen from the above data, external NDCT phenes in young people were manifested by skeletal, skin, articular forms and the presence of small developmental anomalies. In terms of severity, they were manifested by hypermobility of the joints (100%), a change in the shape of the spine (44%), chest (43.8%), skin elongation of varying severity (38.8%), small developmental anomalies (21.1%) and flat feet (20.4%). The frequency of combinations of different hair dryers in patients was different, a combination of 6 external hair dryers was detected in 5 (4.5%), 5 - in 11 (10%), 4 - in 21 (20%), 3 - in 26 (24.3%), 2 - in 31 (30.6%) examined, and in 11 (10%) patients, one hair dryer was identified (Fig. 8).

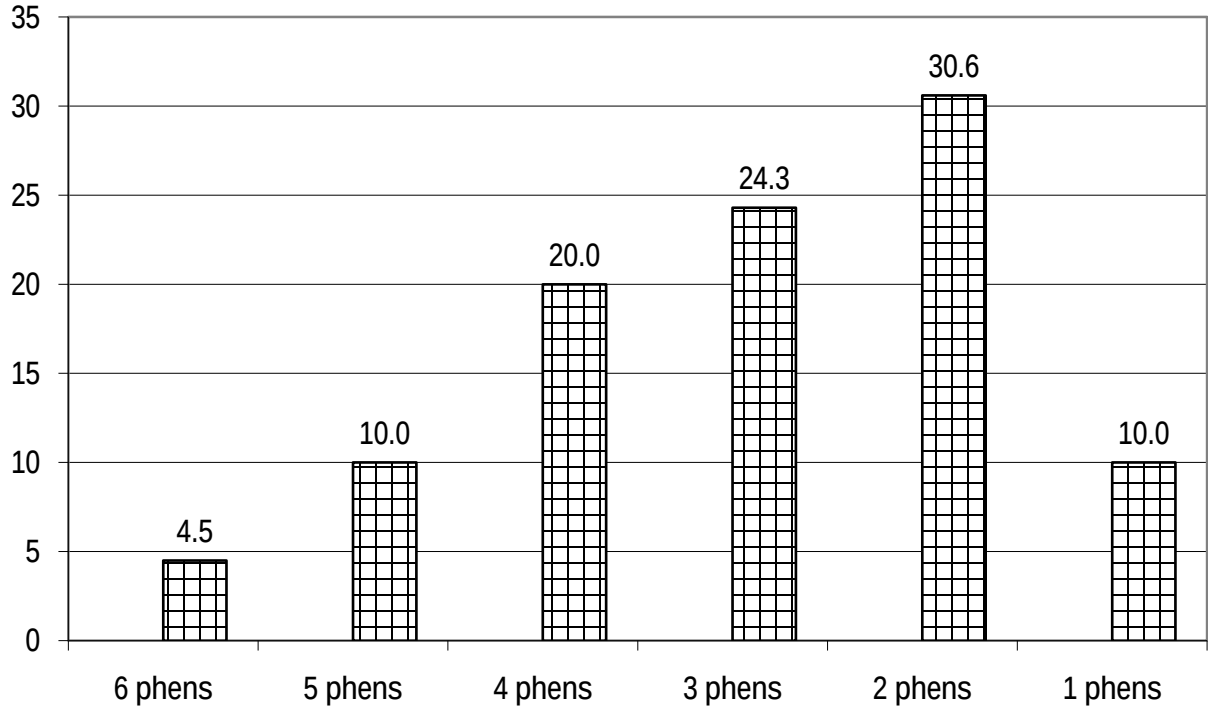

Figure 8. Frequency of occurrence of combinations of various external hair dryers in patients with NDCT.

Analysis of internal phenes in patients with NDCT, depending on its severity, showed that ocular manifestations are characterized by the development of various degrees of myopia in 26 patients. So, in patients, the first degree of myopia was detected in 25 (23.7%), the second degree - in 3 (3.1%) patients (Fig. 9).

DOI: 10.37200/IJPR/V24I2/PR200434
Received: 20 Dec 2019 | Revised: 05 Jan 2020 | Accepted: 18 Jan 2020

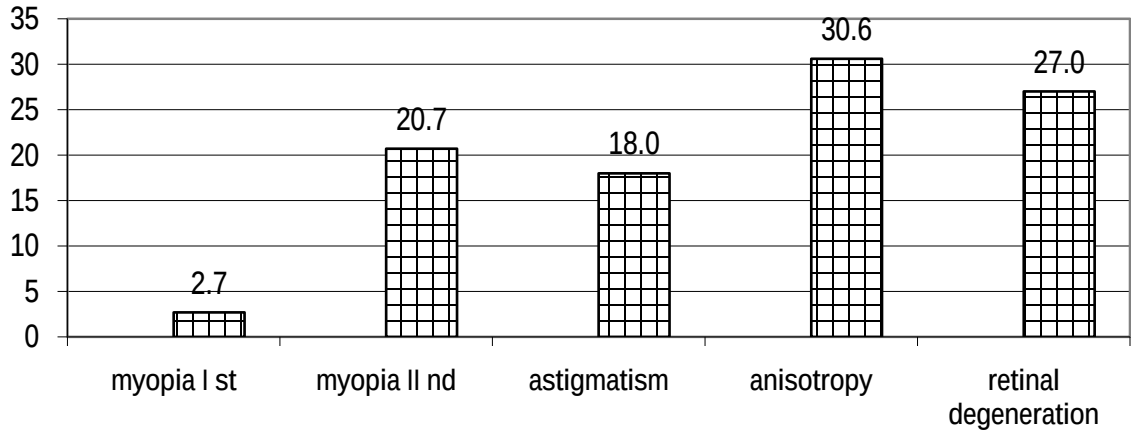

Figure 9. Frequency of lesions of the organ of vision in patients with NDCT

In patients with NDCT, the 1st degree of myopia was established in 3 (2.7%), the 2nd degree - in 22 (20.7%) patients examined. Moreover, astigmatism was detected in 19 (18%) patients, anisometropia in 32 (30.6%) and degenerative changes in the retina in 28 (27%).

As can be seen from the above data, the frequency of damage to the organs of vision was significantly highest in patients with NDCT, which indicates a severe course of the underlying disease. Confirmation of this is the presence of concomitant pathologies. So, chronic bronchitis was detected in 10%, pyelonephritis - 7.2%, nephroptosis of both kidneys of the 1st and 2nd degree - 11.7%, biliary dyskinesia - 22.5%, vegetative-vascular dystonia - 62, 2% in patients with NDCT (Fig. 10).

Of particular note is the presence of gastroduodenal pathology (5.4%), liver pathology (1.8%), osteochondrosis of the lumbar vertebra (1.8%), anemia (7.2%), rheumatoid arthritis (1.8%) andothers.

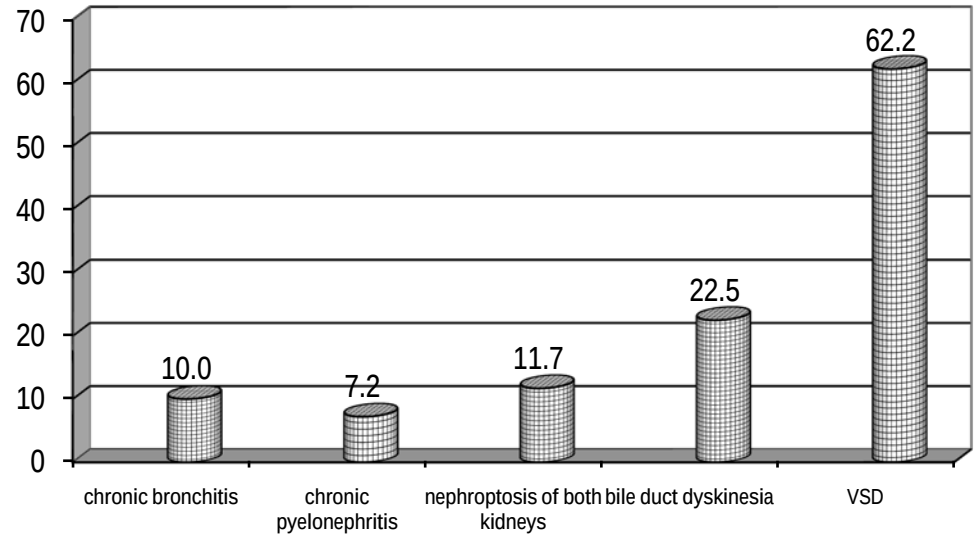

Figure 10. Frequency of concomitant pathologies in patients with NDCT.

DOI: 10.37200/IJPR/V24I2/PR200434
Received: 20 Dec 2019 | Revised: 05 Jan 2020 | Accepted: 18 Jan 2020

III. DISCUSSION

Analyzing the clinical manifestations of NDCT in patients, it should be said that external NDCT phenes were manifested by bone-skeletal, skin, articular forms and the presence of small developmental anomalies. And also, in patients with NDCT, internal phenes are revealed, manifested by damage to the organs of vision, cardiovascular and pulmonary systems, pathology of the organs of the abdominal cavity and kidneys, and especially the ANS. The frequency of occurrence depends on socially significant living conditions, age and gender of patients, the degree of clinical manifestation depends on the late diagnosis of the disease.

IV. CONCLUSION

Thus, the early detection of signs of NDCT in young people among the Uzbek population, as well as the study of the mechanism of their development, the method of studying the HLA system will optimize early diagnosis and predict the outcome of the disease, see a single systemic defect in connective tissue, conduct dispensary registration, timely treatment and prevention possible complications.

REFERENCES

1. Belyaev O. V., Vishnevskaya O. I. Syndrome of systemic dysplasia of connective tissue in childrenwith bronchopulmonary pathology // Vestnik RSMU. - 2015. - 3 (42) - P.121.
2. Bugaeva I.V., Vasilieva O.V. Connective tissue dysplasia is an urgent problem of modern medicine (literature review) \\ ultrasound perinatal diagnostics.-2012.-№27 \ 28.-p.266-281
3. Bugaeva I.V., Vasilieva O.V. Connective tissue dysplasia is an urgent problem of modern medicine (literature review) \\ ultrasound perinatal diagnostics.-2012.-№27 \ 28.-p.266-281.
4. Vereshchagin G.N. Systemic dysplasia of the connective tissue. Clinical syndromes, diagnosis, treatment approaches: a manual for doctors.- Novosibirsk: Novosibirsk State Medical University, 2018.- 37. (p23-31).
5. Gnusaev S.F. Syndrome of connective tissue dysplasia of the heart in children // Attending physician.- 2010.- No. 8.- P.40-44.
6. Dedova V.O., Dotsenko N.Ya., Boev S.S. et al. The prevalence of connective tissue dysplasia (literature review) // Medicine and Education in Siberia.- 2011.- No. 2.- P.123-129.
7. Domnitskaya T. M. Abnormally located chords. M .: Medical practice. 2017.- 95 p.
8. Zemtsovsky E.V. Undifferentiated connective tissue dysplasia. State and prospects of development of ideas about hereditary disorders of connective tissue // Dysplasia of connective tissue. - 2016. - No. 1. - S. 5–9.
9. Kadurina T.I., Gorbunova V.N. Connective tissue dysplasia .-- St. Petersburg: ELBI, 2013 .-- 714 p.
10. Komissarova L.M., Karachaev AN., Kesova M.I. The course of pregnancy and childbirth with connective tissue dysplasia // Obstetrics and gynecology.- 2012.- No. 3.- P.4-8.
11. Moses V.G., Ushakova G.A. Systemic manifestations of connective tissue dysplasia in women with varicose veins of the pelvis // Obstetrics and Gynecology.- 2016.- No. 2.- P.42-44.
12. Nechaeva G.I., Viktorova I.A. Connective tissue dysplasia: terminology, diagnosis, management tactics.- Omsk, 2015.- 188s.
13. Nesterenko Z. V. Classification concepts of connective tissue dysplasia // Health of a child.- 2015.- No. 5 (26) .- P.131-135
14. Nechaeva G.M., Yakovlev V.M., Konev V.P. and other Connective tissue dysplasia: the main clinical syndromes, the diagnosis, treatment // The attending physician.- 2018.- No. 2.- P.22–28.
15. Nechaeva G.I. et al. To the problem of connective tissue dysplasia in the pathology of the cardiovascular system in children. Journal “Child Health” 4 (7) 2015.- p. 20-24
16. Nikolaev K.Yu., Oteva E.A., Nikolaeva A.A. and other Connective tissue dysplasia and multiple organ pathology in school children // Pediatrics.- 2016.- No. 2.- P.89-92.
17. Ostropolets S.S. To the problem of connective tissue dysplasia in the pathology of the cardiovascular system in children // Children's Health .- 2017.- No. 4 (7) .- P.15-20.

DOI: 10.37200/IJPR/V24I2/PR200434
Received: 20 Dec 2019 | Revised: 05 Jan 2020 | Accepted: 18 Jan 2020

18. Ponomarenko Yu.V. Hypermobility of joints in the syndrome of undifferentiated connective tissue dysplasia // Kazan Medical Journal.- 2017.- T.88, No. 5. (adj.) .- P.15-17.
19. Perekalskaya M.A., Makarova L.I., Vereshchagina G.N. Neuroendocrine dysfunction in women with systemic dysplasia of the connective tissue // Clinical Medicine.– 2012.– T.80, No. 4.– P.48–51
20. Smolnova T.Yu., Buyanova S.N., Savelyev S.V., Petrova V.D. Connective tissue dysplasia as one of the possible causes of urinary incontinence in women with genital prolapse // Urology. - 2014. - No. 2. - P.25 - 30.
21. Spivak E.M. Joint hypermobility syndrome in children and adolescents: Monograph.- Yaroslavl, 2013.- 128c
22. Tyabut T.D., Karatysh O.M. Undifferentiated connective tissue dysplasia // Modern rheumatology.- 2014.- No. 2.- P.19-23.
23. Filipenko P.S., Malookaya Yu.S. The role of connective tissue dysplasia in the formation of mitral valve prolapse // Klin.meditsina.- 2012.- T.84 (12) .- P.13–19.
24. Tsukanov Yu.T., Tsukanov A.Yu. Varicose veins of the lower extremities as a result of connective tissue dysplasia // Angiology and Vascular Surgery. - 2014. - T. 10, No. 2. - S. 84 - 89.
25. Shilyaev R.R., Shalnova S.N. Connective tissue dysplasia and its connection with the pathology of internal organs in children and adults // Vopr. modern pediatrics. - 2013. - No. 5 (2). - S. 61–67.
26. Shodikulova G.Z. Markers of endothelial function and antioxidant system in assessing undifferentiated dysplasia of connective tissue in patients with congenital mitral valve pololapse // Postgraduate Doctor. - 2012. - T. 54. - No. 5.1. - S. 217-223.
27. Shodikulova G.Z., Tashkenbaeva E. N. The state of endothelial function and the protective effect of magnesium ions (Mg 2) in patients with undifferentiated dysplasia of the connective tissue with congenital mitral valve prolapse // News of problems of biology and medicine. - 2012. - T. 2. - No. 2.Arroyo-Avila M., Vila L.M. Cardiac tamponade in a patient with mixed con-nective tissue disease // J. Clin. Rheuma-tol. 2015. Vol. 21, № 1. P. 42-45.
28. Babamuradova Z. B., Shodikulova G. Z., Mirzaev O. V. Treatment of patients with undifferentiated connective tissue dysplasia in mitral valve prolapse with varying degrees of mitral regurgitation //European science review. – 2018. – №. 3-4. C.140-143
29. Bennett R. Overlap syndromes. In: Firestein G, Budd RC, Gabriel SE, McInnes IB, O'Dell JR, editors. Kelley's Textbook of Rheumatology. 9th ed. Philadelphia, PA: Elsevier Inc; 2013. pp. 1431–1451
30. Castori M., Morlino S., Ghibellini G., Celletti C., Camerota F., Grammatico P. Connective tissue, Ehlers-Danlos syn-drome(s), and head and cervical pain // Am. J. Med. Genet. C. Semin. Med. Ge-net. 2015. Vol. 169, № 1. P. 84-96.
31. Conti V, Esposito A, Cagliuso, et al. Undifferentiated connective tissue disease-An unsolved problem: Revision of literature and case studies. International Journal of Immunopathology and Pharmacology. 2010;23(1):271–278.
32. Deng Y., Wei S., Hu S., Chen J., Tan Z., Yang Y. Ehlers-Danlos syndrome type IV is associated with a novel G984R COL3A1 mutation // Mol. Med. Rep. 2015. Vol. 12, №1. P. 1119-1124.
33. Guerrero LF1, Rueda JC, Arciniegas R, Rueda JM. Undifferentiated connective tissue disease in a rheumatology center in Cali, Colombia: clinical features of 94 patients followed for a year. Rheumatol Int. 2013 Apr;33(4):1085-8.
34. Hajas A, Szodoray P, Nakken B, Gaal J, et al. Clinical Course, prognosis, and causes of death in mixed connective tissue disease. J Rheumatol. 2013;40(7):1134–1142.
35. Jensen S.A., Aspinall G., Handford P.A. C-terminal propeptide is required for fi-brillin-1 secretion and blocks premature assembly through linkage to domains cbEGF41-43 // Proc. Natl. Acad. Sci USA. 2014. Vol. 111, №28. P. 10155-10160.
36. Mosca M., Tani C., Vagnani S., Bom-bardieri S. The diagnosis and classifica-tion of undifferentiated connective tissue diseases // J. Autoimmun. 2014. Vol. 48-49 P. 50-52.
37. Shodikulova G. Z. Effect of L-arginine on endothelial dysfunction in patients with congenital mitral valve prolapse //Kazan medical journal. – 2014. – T. 95. – №. 3. – C. 326-331.
38. Shodikulova G. Z., Toirov E. S., Babamuradova Z. B. Clinical biochemical features in patients with undifferentiated connective tissue dysplasia //European science review. – 2016. – №. 1. – C. 129-131.
39. Shodikulova G. Z. Special features of clinical and functional disorders in patients with undifferentiated connective tissue dysplasia //European science review. – 2017. – №. 3-4. – C. 72-74.
40. Shodikulova G. Z. Value of matrix metalloproteinases and their tissue inhibitors in the diagnosis of undifferentiated connective tissue dysplasia //The First European Conference on Biology and Medical Sciences. – 2014. – C. 111-116.

DOI: 10.37200/IJPR/V24I2/PR200434
Received: 20 Dec 2019 | Revised: 05 Jan 2020 | Accepted: 18 Jan 2020

41. Tani C., Carli L., Vagnani S., Talarico R., Baldini C., Mosca M. et al. The diagnosis and classification of mixed con-nective tissue disease // J. Autoimmun. 2014. Vol. 48-49. P. 46-49.
42. Sung Y.K., Chung L. Connective tissue disease-associated pulmonary arterial hypertension. Rheum // Dis. Clin. North. Am. 2015. Vol. 41, №2. P. 295-313.
43. Ueshima *K.* Magnesium and ischemic heart disease: a review of epidemiological, experimental, and clinical evidences //Magnes Res.- 2005.- Vol.18 (4).- P.275–284.
44. Wang X.L., Mahaney M.C., SimA.S.,Genetic contribution of the endothelial constitutive nitric oxide synthase gene to plasma nitric oxide levels // Arterioscler. thromb. vasc. biol. – 1997. – Vol. 17. – P. 3147–3153.
45. Yosefy C., Ben Barak A. Floppy mitral valve/mitral valve prolapse and genetics //J. Heart Valve Dis.- 2007.- Vol.16 (6).- P.590-595.
46. Zacchigna L., Vecchione C., Notte A., Cordenonsi M., et al. Emilin1 links TGF–beta maturation to blood pressure homeostasis //Cell.- 2006.- Vol.124(5).- P.929–942.

DOI: 10.37200/IJPR/V24I2/PR200434
Received: 20 Dec 2019 | Revised: 05 Jan 2020 | Accepted: 18 Jan 2020