

## The Prevalence of Undifferentiated Connective Tissue Dysplasia in Senior Students

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### ABSTRACT

*Background.* Connective tissue dysplasia is an important medical condition requiring attention and research.

*The aim.* To analyse the prevalence of the clinical signs of undifferentiated connective tissue dysplasia among senior students of educational institution.

*Methods.* 110 senior students (average age - 20 years) were examined (females 64 %, males 36 %). Joint hypermobility was assessed according to the Bayton scale, joint hypermobility syndrome according to the Brighton criteria. The main criteria for undifferentiated connective tissue dysplasia and the stigma of dysembryogenesis were studied: flat feet; deformities of the spine, chest; visual impairment etc. The state of the cardiovascular system and gastrointestinal tract was assessed by questioning and anamnestic data.

*Results.* Joint hypermobility was the most common feature of undifferentiated connective tissue dysplasia, accounting for 62.7%. Malocclusion occurred in 36.8% of cases, visual impairment occurred in 32.7%, myopia in 21.8%, astigmatism in 4.5%, strabismus in 3.7%, and a combination of astigmatism and myopia in 2.7%. Abnormalities in the development of the dentition of the jaws were found in 29.1% of students. Deformities of the feet with a decrease in the longitudinal arch were diagnosed in 21.8% and spinal axis deviations in 21%.

*Conclusions.* Undifferentiated connective tissue dysplasia in senior students was most often manifested by joint hypermobility, visual impairment, malocclusion, flat feet, scoliotic deformities, and multiple stigmata of dysembryogenesis.

**Keywords:** connective tissue dysplasia, joint hypermobility, diagnostics, students, stigma of dysembryogenesis, rehabilitation.

### INTRODUCTION

The history of connective tissue dysplasia dates back to ancient times, but its systematic study began only in the second half of the eighteenth century (Maquart & Borel, 2012). In the past certain physical signs related to the complex structure of connective tissue were observed. For example, historical records indicate that in

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some cultures, great importance was placed on people with extraordinary flexibility and joint hypermobility (Talarico et al., 2020).

Connective tissue dysplasia is an important medical condition requiring attention and research. It is a group of genetically determined diseases characterised by abnormalities in connective tissue structure and function (Antunes et al., 2019), (Protsailo et al., 2023). The combination of abnormalities in collagen fibres, elastin, fibronectin, and other connective tissue components leads to a variety of clinical manifestations and complications. This disease can affect different organ systems, including the skin, joints, cardiovascular, nervous, and visual organs (Bandzerewicz & Gadomska-Gajadhur, 2022). This group of diseases includes common syndromes such as Marfan syndrome, Edler-Danlos syndrome, osteogenesis imperfecta type I and multiple epiphyseal dysplasia. Current research in connective tissue dysplasia has been a key factor in understanding the aetiology, pathogenesis and treatment of these conditions. Despite significant advances in molecular genetics and biomedical research, many aspects of these diseases remain poorly understood (Meester et al., 2017).

This disease in children and adolescents is a serious medical problem that requires proper attention and research. This condition is characterised by disorders in the structure and function of connective tissue, which is the basis for the proper development of organs and tissues during childhood and adolescence. Connective tissue dysplasia can have a significant impact on the physical development and overall health of young patients (Zeigler et al., 2021). In children and adolescents, connective tissue dysplasia can cause a variety of clinical manifestations, which may include changes in the structure of bones, joints, skin, and the cardiovascular system. This can be manifested through joint flexibility, lack of joint stability, increased vulnerability to injury, problems with bone growth, and other signs that can affect the quality of life and ability to engage in physical activity (Tofts et al., 2009). Genetic factors, external influences and other factors can affect the formation and functioning of connective tissue in a young body. Understanding these factors is important for developing effective strategies for the diagnosis, treatment and prevention of connective tissue dysplasia in children and adolescents (Harsanyi et al., 2020).

In the case of musculoskeletal disorders, people are recommended a set of rehabilitation means aimed at preventing and restoring functions, this includes prevention of risk factors of dysplasia, improvement of the functioning of the musculoskeletal system, and correction of the imbalance between muscles (Lewis et al., 2019). Each set of therapeutic exercises should include exercises for the major muscle groups of the trunk and extremities as well as exercises for weakened muscle groups, which will improve the overall performance of the whole body (Van Criekinge et al., 2019). It is very important to maintain the correct physiological

curvature of the spine, to strengthen back muscles, abdominals and gluteal muscles (Lee et al., 2022). The aim of this study was to analyse the clinical signs of undifferentiated connective tissue dysplasia among senior students of educational institution and compare them with the main characteristics defined by researchers.

## METHODS

**Participants.** One hundred and ten fourth- and fifth-year students of the I. Horbachevsky Ternopil National Medical University took part in the survey. The mean age of the students was  $20,15 \pm 2,23$  years (70 (63.6%) females, 40 (36.4%) males).

**Inclusion criteria.** The selection was conducted among fourth- and fifth-year students studying at the Faculty of Medicine of the I. Horbachevsky Ternopil National Medical University and members of the student scientific club, anonymously and voluntarily. All participants were free to withdraw from the study at any time without giving any reason.

**Exclusion criteria.** All students could take part in the study without any restrictions. All students took part in the study voluntarily.

**Outcomes.** The examination of joint hypermobility is conducted according to the Beighton scale and joint hypermobility syndrome according to the Brighton criteria (Malek et al., 2021), as recommended 1-2 points are physiological norm, 3-4 – mild hypermobility, 5-8 – moderate hypermobility, 9 – severe hypermobility.

No student with differentiated connective tissue dysplasia was found, so the main criteria for undifferentiated connective tissue dysplasia and the stigma of dysembryogenesis were studied: flat feet; deformities of the spine, chest; visual impairment; deformities of the earlobe; dental anomalies; vascular malformations; gallbladder deformities; mitral valve prolapse. Deformities of the spine were detected by examination from three sides - anterior, posterior and lateral. The spinal axis in the thoracic, cervical and lumbar spine, symmetry of the upper arms, waist triangles, thoracic kyphosis and lumbar lordosis were assessed. The condition of the cardiovascular system and gastrointestinal tract was assessed by interview and medical history.

## RESULTS

From 110 senior medical students' joint hypermobility was detected in 69 persons (62.7%). In most cases, signs of joint hypermobility were manifested on the fingers. Thus, passive flexion of the 1st finger towards the forearm during bending at the radiocarpal joint and passive flexion of the metacarpophalangeal joint of the 5th finger in both directions accounted for 75% and 76% of cases, respectively (Fig. 1).



**Fig. 1. Hypermobility of the thumb and metacarpophalangeal joint of the 5th finger**

Over-extension of the elbow joint by more than 10 degrees was observed in 56% of cases, over-extension of the knee joints by more than 10 degrees was rare, no more than 6% (Fig. 2).



**Fig. 2. Over-extension (recurvature) of the knee joints. Bilateral flat feet**

One student was able to bend forward with fixed knee joints, with palms reaching the floor plane - 0.7% (Table 1).

**Table 1. Structure of joint hypermobility combinations according to anatomical location**

	Anatomical location	Number of cases in %.	Number of cases in absolute figures
1	Little finger	74.5	82
2	First finger	76.3	84
3	Elbow joint	37.2	41
4	Knee joint	6.3	7
5	Spine	0.9	1

According to Bayton's criteria, 26 students (23.6%) had a physiological norm of 1-2 points.

A mild degree of hypermobility of the joints of the upper extremities dominated. Average indicators were inherent in the average degree of joint hypermobility and only one student had a severe degree of hypermobility (Table 2).

**Table 2. Severity of joint hypermobility according to the Bayton scale**

	The degree of hypermobility	Cases		Points
		%	N	
1	Physiological norm	23.6	26	1-2
2	Mild hypermobility	68.2	75	3-4
3	Medium hypermobility	7.3	8	5-8
4	Severe hypermobility	0.9	1	> 9
5	<b>Total</b>	<b>100 %</b>	<b>110</b>	

Visual impairment was diagnosed in 36 (32.7%) cases. The students used glasses or contact lenses to correct their vision or did not use them in case of minor manifestations. Myopia accounted for 21.8%, astigmatism - 4.5%, strabismus - 2.7%, and a combination of astigmatism and myopia - 2.7%. Information about the state of vision was collected through a survey (no special vision tests were performed).

One student had Stilling-Turk-Duane syndrome. This congenital rare type of strabismus is most often characterised by the inability of the eye to move outward (Fig. 3).



**Fig. 3. Stilling-Turk-Duane syndrome with undifferentiated connective tissue dysplasia. The inability of the left eye to move outwards (student K)**

An incorrect bite was observed among 36 students (32.7%), and every sixth used braces to correct the dentition of the jaws. Among the foot deformities, longitudinal flat feet were most diagnosed, with a decrease in lower limb muscle tone accounting for 21.8%. The condition of the feet was assessed clinically, without X-ray examination.

Spinal deformities were detected by examination from three sides - front, back, and side. The spinal axis in the thoracic and lumbar spine, symmetry of the upper arms, waist triangles, thoracic kyphosis and lumbar lordosis were assessed. Thoracic scoliosis was detected in 70.0%, thoracolumbar scoliosis in 12.2%, and S-shaped scoliosis in 7.8%. X-ray examination was not performed, only in some cases with severe spinal curvature a spondylogram was recommended. Scoliotic deformity was detected in 21.8 % of students.

**Clinical case 1.** A student, M. 22 years old. Engaged in sports – gymnastics. Recently, he has developed back pain that worsens with physical activity. On examination – athletic build, with relief muscles, medium height. Excessive mobility of the elbow and knee joints – mild hypermobility (4 points). The spinal axis in the thoracic spine is deviated to the right, and a gentle rib hump is contoured when bending forward. Pressing on the paravertebral areas of the thoracic and lumbar spine causes pain. The ears are flattened, the earlobe is oblique. The nose is elongated, thin, and the lower jaw is depressed. Two years ago he was operated on for varicocele. He has varicose lesions – haemorrhoids. He suffers from gastritis and gallbladder dysfunction. For four years he was treated for the astheno-depressive syndrome.

Magnetic resonance imaging of the thoracic and lumbar spine revealed degenerative changes, chondrosis, and spondyloarthrosis. Bulging of intervertebral discs of the thoracic spine with numerous cartilaginous Schmorl's nodes, wedge-shaped deformity of the bodies of 7-11 thoracic vertebrae. Right-sided thoracic kyphoscoliosis, grade 2. At the level of the lumbar spine, left-sided scoliosis, grade 2,

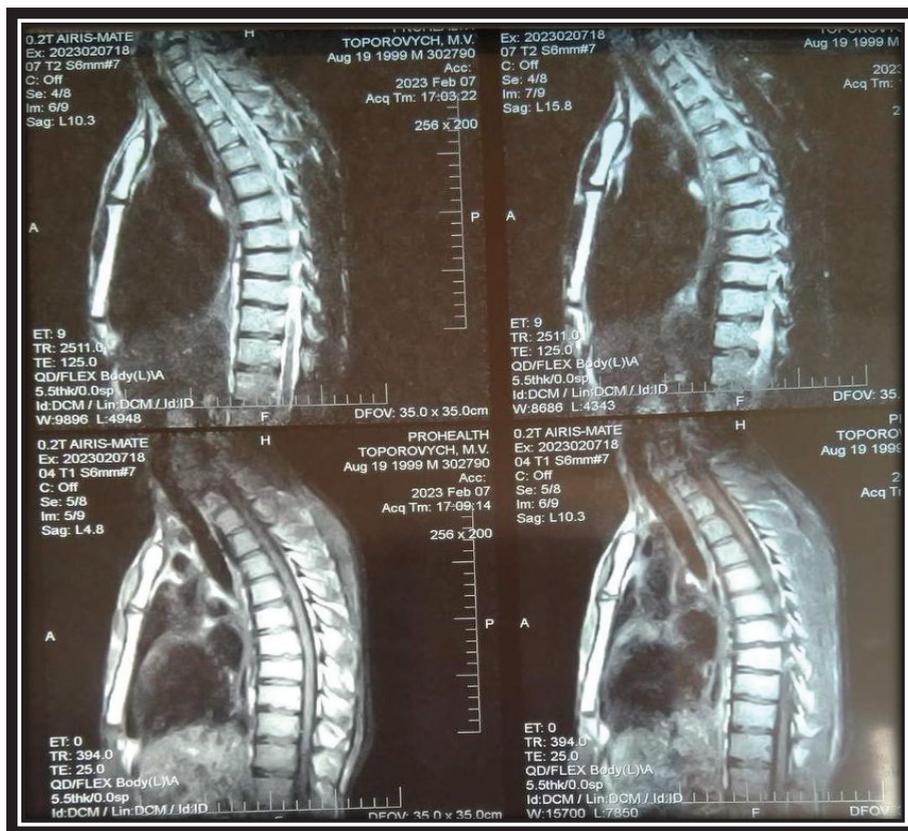


Fig. 4. MRT imaging of the thoracic spine. Osteochondrosis of the spine (student M) numerous Schmorl's cartilage nodes, protrusion of the intervertebral discs L1-L2, L2-L3, dorsal prolapse of the L3 intervertebral disc, left-sided dorso-lateral protrusion of the L4-L5 intervertebral discs (Fig. 4).

The anamnesis is burdened. The father (55 years old) was operated on for haemorrhoids and varicocele. He suffers from hypertension. He had a myocardial infarction. Wears glasses - myopia. He has severe varicose veins of the lower extremities, gastritis, gallbladder dysfunction, urolithiasis. Has osteochondrosis of the spine with pain syndrome. Clinic of the undifferentiated connective tissue dysplasia. Mother (50 years old). Suffers from urolithiasis, hypertension, varicose veins of the lower extremities, back pain, heel spurs – signs of undifferentiated connective tissue dysplasia. She was operated on for cervical erosion (papillomatosis). Sister (27 years old). Suffers from urolithiasis, gastritis, gallbladder dysfunction, depressive syndrome.

Clinical diagnosis. Dysplastic right-sided thoracic scoliosis, grade 2. Spondyloarthrosis of the thoracic and lumbar spine with pain. Hemorrhoids. Varicocele – condition after surgery. Urolithiasis is a condition. Gallbladder dysfunction. Astheno-depressive syndrome. Joint hypermobility syndrome on the background of undifferentiated connective tissue dysplasia.

Abnormalities of the ear shell (oblique earring) accounted for 12.6 % of cases, which is one of the phenotypic manifestations of undifferentiated connective tissue dysplasia.

The state of the cardiovascular system was assessed by interviewing and taking anamnesis data. Such changes were not frequent (12.6%), namely arrhythmia, tachycardia, mitral valve prolapse, and high or low blood pressure. One student was operated on in childhood for a defect in the heart septum. Biliary dyskinesia, nervous flow, and chest deformity accounted for 1.1% of cases each.

**Clinical case 2.** In this case, there was a classic picture of a family predisposition to undifferentiated connective tissue dysplasia, manifested by various clinical signs. According to scientists, the manifestations of undifferentiated connective tissue dysplasia are multifaceted, ranging from mental disorders to autonomic dysfunction, chronic fatigue syndrome, myopia, skeletal, renal, cardiac valve and functional disorders of the immune, respiratory and other systems.

Thus, the student-athlete had thoracic scoliosis, osteochondrosis and a number of other pathologies: haemorrhoids; varicocele; urolithiasis; gallbladder dysfunction; astheno-depressive syndrome; and joint hypermobility syndrome. These diseases are the overwhelming majority of the components of undifferentiated connective tissue dysplasia. According to the Brighton criteria, the diagnosis of joint hypermobility syndrome requires the presence of 2 major criteria, or 1 major and 2 minor criteria, or 4 minor criteria.

Our student had two major criteria: joint hypermobility of 4 points on the Bayton scale; spinal osteochondrosis with pain; and several minor criteria - haemorrhoids, varicocele. These signs are sufficient to diagnose this syndrome. As auxiliary phenotypic manifestations of undifferentiated connective tissue dysplasia, abnormalities of the ear shell (oblique earring, cup-shaped ear, underdevelopment of a part of the curl, cone-shaped, boat-shaped curl deformity, loss of the lower curl, transverse ear cleft...) are rare and do not exceed 12 %, which is consistent with our observations.

Autonomic dysfunction, biliary dyskinesia, functional and anatomical changes in the heart in undifferentiated connective tissue dysplasia reach up to 70% of cases. since, in our case, the diagnosis of these ailments was carried out by interview and anamnesis, such changes were not frequent - 12.6%, namely arrhythmia,

tachycardia, mitral valve prolapse, increased or decreased blood pressure, biliary dyskinesia.

These diseases can have a latent course, which the patient may not be aware of, so basic examinations (ECG, ultrasound) will help to identify these abnormalities. The main areas of therapy for undifferentiated connective tissue dysplasia are the complex approach of various specialists: orthopedists, surgeons, gastroenterologists, psychologists, neurologists, dentists, cardiologists, cosmetologists. Treatment is usually symptomatic; etiopathogenetic treatment has not been developed at the present stage of medicine.

The main emphasis is on diet therapy, massage, physiotherapy, exercise therapy, psychotherapy). Among drug therapy, the following agents are recommended to stimulate collagen formation: chondroitin sulfate, ascorbic acid, B vitamins, trace elements (copper, zinc, magnesium).

## DISCUSSION

There is considerable disagreement regarding the criterion of joint hypermobility and its interpretation and frequency of detection. In children under 2-3 years of age, joint hypermobility is 50%, in children aged 15 years 34%, and in adults 10-15%.

Among 110 examined senior medical students, hypermobility of any degree of joint severity was found in 84 future doctors (76.3%), which does not contradict the data of other authors. (Butt et al., 2023), (Reuter & Fichthorn, 2019).

Visual impairment, visual disorders were diagnosed in 32,7 % of cases, 22 % of students had myopia. Myopia and eye abnormalities were observed in 11 %. Perhaps, the high visual load of senior students is the reason for the increased frequency of visual disorders when compared to children under 15 years of age. One of these factors can be the normal age-related changes that occur throughout our lives, and they can affect the way we see and process visual information (Ciner et al., 2023). Association between visual and cognitive impairments, studies (Jiang & Zhou, 2023) have shown a strong association between visual and cognitive impairments, with visual impairment being more likely to lead to cognitive decline. Also, visual health in students may be influenced by educational pressures and school entrance age has been associated with visual impairment (Ding et al., 2023).

During the survey, we found one fifth-year student, aged 21, with Stilling-Turk-Duane syndrome, also known as Duane Retraction Syndrome (Kocamaz et al., 2019). Stilling-Turk-Duane syndrome is a rare congenital type of strabismus, most often characterised by the inability of the eye to move outwards. There is an imbalance of the eye muscles due to atrophy of the nuclei of the optic nerve that

innervates the lateral rectus muscle. The cause of this condition is a mutation of the *Sal-like4* gene (*SALL4*). Boys are more often affected – 60%, girls – 40%. Unilateral involvement is typical – 78%, left eye – 71.9%. In our observation of this rare form of strabismus, the clinical signs fully correspond to the data of many scientists: unilateral lesion; left eye; male gender.

The shape of the dental bite, malocclusion, is an easily identifiable phenotypic sign of undifferentiated connective tissue dysplasia. Since, in our case, more than 64 % of the subjects were female students with malocclusion, they are more careful about correcting dental anomalies both in terms of cosmetics and function, we believe that the frequency of this deformity reached 32.7%.

According to the literature, (Vergillos Luna et al., 2023) flat feet are quite common among children, with a prevalence of up to 44% in preschool-aged children. Since the condition of the feet of students was assessed clinically, without X-ray examination, the rate of foot deformity was much lower – 21.8%, mainly longitudinal flat feet against the background of decreased lower limb muscle tone. For a more accurate diagnosis of the condition of the feet, in some cases, an X-ray examination was recommended, after which the percentage of detection of this disease would increase significantly.

Most often, spinal curvature among students was diagnosed in the thoracic spine during the examination, which does not contradict the literature (Deyun et al., 2023). In their study most often, spinal curvature among students was diagnosed in the thoracic spine during examinations. The incidence of abnormal spinal curvature in students increased with age, with higher rates in senior high school students compared to primary school students. Female students had a higher detectable rate of spinal curvature compared to male students. Factors influencing abnormal spinal curvature included the phase of studying, nutritional status, and time spent engaged in outdoor activities. Students who participated in our study, in other parts of the spine had curvature in no more than 12.2% of cases. Scoliotic deformity was detected in 21.8% of students, which is consistent with the data of other scientists – 20%. This assessment was conducted during the survey using generally accepted clinical examination methods.

Further research to find the main phenotypic features of undifferentiated connective tissue dysplasia is the main step towards reliable and early detection of this disease.

## CONCLUSIONS

The data obtained emphasise the diversity of clinical manifestations of undifferentiated connective tissue dysplasia affecting various body systems.

In summary, undifferentiated connective tissue dysplasia has a wide range of clinical features, which emphasises the importance of a comprehensive approach to diagnosis and treatment. Understanding this variability is crucial to ensure effective care and support for people with this disease.

**ORCID and contributionship:** A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article. Mykhailo. D. Protsailo: 0000-0003-1710-3172 <sup>A, B,D,E,F</sup> Volodymyr. G. Dzhyvak: 0000-0002-4885-7586 <sup>A, B,C,D,E</sup> Ihor. O. Krycky: 0000-0003-0469-2684 <sup>A,E</sup> Pavlo. V. Hoshchynskyi: 0000-0002-5849-0335 <sup>C,F</sup> Ihor M. Horishnyi: 0000-0002-7109-4652 <sup>E</sup> Iryna B. Chornomydz: 0000-0002-9797-7891 <sup>B</sup>

#### CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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## Nediferencijuotos jungiamojo audinio displazijos paplitimas tarp vyresniųjų kursų studentų

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### SANTRAUKA

*Tyrimo pagrandimas.* Jungiamojo audinio displazija yra svarbi medicininė būklė, reikalaujanti dėmesio ir tyrimų.

*Tikslas* – išanalizuoti nediferencijuotos jungiamojo audinio displazijos klinikinių simptomų paplitimą tarp ugdymo įstaigos vyresniųjų kursų studentų.

*Metodai.* Ištirta 110 vyresniųjų kursų studentų (amžiaus vidurkis – 20 metų) (64 proc. moterų, 36 proc. vyrų). Sąnarių hiperomobilumas vertintas pagal Baytono skalę, sąnarių hiperomobilumo sindromas – pagal Brightono kriterijus. Tirti pagrindiniai nediferencijuotos jungiamojo audinio displazijos ir stigos disempliacijos kriterijai: plokščiapėdystė, stuburo, krūtinės ląstos deformacijos, regos sutrikimai ir kt. Širdies ir kraujagyslių sistemos bei virškinamojo trakto ligos buvo vertinamos apklausos ir anamnestiniais duomenimis.

*Rezultatai.* Sąnarių hiperomobilumas buvo dažniausias nediferencijuotos jungiamojo audinio displazijos požymis, sudarantis 62,7 proc. atvejų. Netaisyklingas sąkandis pasireiškė 36,8 proc. atvejų, regos sutrikimai – 32,7 proc., trumparegystė – 21,8 proc., astigmatizmas – 4,5 proc., strabizmas – 3,7 proc., astigmatizmas ir trumparegystė – 2,7 proc. Dantų vystymosi sutrikimai nustatyti 29,1 proc. atvejų. Pėdų deformacijos, kai sumažėja išilginis skliautas, diagnozuotos 21,8 proc. atvejų, o stuburo ašies nuokrypiai – 21 proc.

*Išvada.* Nediferencijuota jungiamojo audinio displazija vyresniųjų kursų studentams dažniausiai pasireiškė sąnarių hiperomobilumu, regos sutrikimais, ydingu sąkandžiu, plokščiapėdyste, skeveldrinėmis deformacijomis ir dauginiais disembriogenezės požymiais.

**Raktažodžiai:** jungiamojo audinio displazija, sąnarių hiperomobilumas, diagnostika, studentai, disembriogenezės stigma, rehabilitacija.

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