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Е.Ф. Котовщикова, Н.С. Сидоровъ

Кафедра пропедевтики внутренних болезней имени проф. З.С. Баркагана,
Федеральное государственное бюджетное образовательное учреждение высшего образования
«Алтайский государственный медицинский университет» Министерства здравоохранения
Российской Федерации, Барнаул, Россия

АНАЛИЗ ВНЕШНИХ ФЕНОТИПИЧЕСКИХ ПРИЗНАКОВ НЕДИФФЕРЕНЦИРОВАННОЙ ДИСПЛАЗИИ СОЕДИНИТЕЛЬНОЙ ТКАНИ В АСПЕКТЕ ПАТОГЕНЕЗА И ВОЗРАСТНОЙ ДИНАМИКИ ТЕЧЕНИЯ ДИСПЛАСТИЧЕСКОГО ПРОЦЕССА

E.F. Kotovshchikova, N.S. Sidorov'

Department of Propaedeutics of Internal Diseases named after prof. Z.S. Barkagana,
Federal State Budgetary Educational Institution of Higher Education «Altai State Medical
University» of the Ministry of Health of the Russian Federation, Barnaul, Russia

Analysis of External Phenotypic Signs of Undifferentiated Connective Tissue Dysplasia in Aspect of Pathogenesis and Age Dynamics of The Course of The Dysplastic Process

Резюме

В статье представлено текущее состояние и проблемы клинической диагностики недифференцированной дисплазии соединительной ткани, основанной на определении внешних фенотипических признаков, при этом постулируется примат клинической диагностики данного состояния. Рассмотрены ассоциированные с данной проблемой термины — фенотипический признак, стигма, малая аномалия развития, врождённый порок развития. Вводится оригинальная концепция диспластического процесса для описания глобальной в популяции и индивидуальной для конкретного пациента динамики состояния изменённого обмена соединительной ткани, которая определяется взаимодействием наследственных и поведенческих факторов, условиями среды и естественным процессом роста и старения организма. Приводится оригинальная классификация внешних фенотипических признаков по категориям принадлежности к системе органов, методике определения, влиянию на клиническую картину, потенциальной динамике признака, частоте встречаемости, отношению к онтогенезу, диспластическому процессу и поражённому элементу соединительной ткани как основа патогенетического анализа их диагностической значимости. В качестве примера применения данного подхода анализируются малые аномалии развития, анамнестические (нарушение гемостаза, травматические эпизоды), субъективные (варианты болевого синдрома), костные (долихостеномелия, костно-хрящевые дисплазии, ограничение разгибания локтевого сустава) и кожные внешние фенотипические признаки, для каждого из которых уточнены методики определения и обозначены возможные ограничения в реальной клинической практике. Для кожных признаков проведена группировка по отношению к основным свойствам кожи, определяемым конкретным структурным элементом соединительной ткани. Для признака повышенной растяжимости предложена альтернативная методика определения манёвром растягивания на плоскости между двумя стандартными штрихами.

Ключевые слова: *соединительная ткань, дисплазия, фенотипический признак, диспластический процесс*

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Abstract

The article presents the current state and problems of clinical diagnostics of undifferentiated connective tissue dysplasia based on the determination of external phenotypic features, while postulating the primacy of clinical diagnostics of this condition. The terms applied to this problem are considered — phenotypic feature, stigma, minor developmental anomaly, congenital malformation. An original concept of the dysplastic process is introduced to describe the global in the population and private for a specific patient dynamic of the course of the state of altered metabolism of connective tissue, which is determined by the interaction of hereditary and behavioral factors, environmental conditions and the natural process of growth and aging of the organism. An original classification of external phenotypic features by categories of belonging to the organ system, determination method, influence on the clinical picture, potential dynamics of the feature, frequency of occurrence, relation to ontogenesis, dysplastic process and the affected element of connective tissue is given as the basis for pathogenetic analysis of their diagnostic significance. As an example of the application of this approach, minor developmental anomalies are analyzed, anamnestic (impaired hemostasis, traumatic episodes), subjective (variants of pain syndrome), bone (dolichostenomelia, osteochondral dysplasia, limitation of elbow joint extension) and skin external phenotypic signs, for each of which the methods of determination are specified and possible limitations in real clinical practice are indicated. For skin signs, a grouping is carried out in relation to the main properties of the skin determined by a specific structural element of connective tissue. For the sign of increased extensibility, an alternative method of determination by a stretching maneuver on a plane between two standard strokes is proposed.

Key words: *connective tissue, dysplasia, phenotypic trait, dysplastic process*

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CD — congenital defect, EPC — external phenotypic character(s), MDA — minor development abnormality, UCTD — undifferentiated connective tissue disease

Currently, diagnosing undifferentiated connective tissue disease (UCTD) is rather an art than an algorithm of actions. A direct consequence of the absence of clear objective diagnostic criteria is the lack of a separate ICD code for this condition, which prevents global medical data comparison and systematic development of unified methodological approach [1]. Code M35.8 (Other specified systemic involvement of connective tissue) recommended by the Russian professional community does not specify UCTD etiopathogenesis and describes a wider group of medical conditions; second, it differs from the global best practices of assigning this patient group code M35.7 (Joint hypermobility syndrome), since joint hypermobility is one of the most specific and well-studied symptoms of UCTD in Western countries. It is widely known that experienced clinicians can visually recognise UCTD patients [2, p. 38]. An additional or alternative approach is an analysis of a full comprehensive examination and a final decision taken by a clinician for each patient individually [3, p. 34]. However, a detailed analysis of all UCTD signs using clinical, genealogic and imaging methods is very time-consuming and expensive, or even impossible if talking about molecular genetic testing. The situation is aggravated by the high incidence of this condition (minimum 20 %) [4], necessitating the wide practical use of diagnostic tools. Therefore, a method with the highest diagnostic value and available for primary care providers in routine settings should be prioritised, i.e. clinical examination of external phenotypic characters (EPC), which is possible due to the biomechanical (shape-generating) function of connective tissue. Minor heart abnormalities show that the number of internal phenotypic characters closely correlates with the number of diagnosed EPCs, and it can be used in clinical diagnostics [5]. This is phenotypic character identification which lays the foundation for all existing diagnostic scales and criteria [6, 7]. However, these diagnostic scales and criteria have not been analysed for their clinical significance; at best, its formal mathematical equivalent was used. Clinical significance of any fact associated with a patient character can be described only in terms of its practical application, which can be either diagnostic or prognostic. For diagnostic purposes, of importance is the association between this fact and implementation of certain links of a pathological process, underlying the condition on question, which cause frequent clinical manifestations, which make it possible to identify them. For prognostic reasons, of importance are the effects of this fact for

the course (quality of life) or outcome of the disease, including the risk of complications.

Currently, phenotypic characteristics and, thus, diagnosis cannot be treated as the key, unlike genetic and biochemical diagnostics [8]. This is related both to genetic heterogenity of disease entities and varied penetration of mutant allels, impact of external factors on gene expression, which creates ambigous connections between genotype and phenotype: different damages to one and the same gene can clinically present as different phenotypes; damages to different genes can have a similar phenotype. However, taking into consideration the multitude of various causes of EPC and their combinations in clinical manifestations in the form of established syndromes can theoretically boost the accuracy of phenotypical diagnosis.

The objective of this article is to identify a group of UCTD-associated EPCs and determine their clinical importance in terms of the course of dysplastic process, as exemplified by several groups of EPCs.

The meaning and justified use of some terms should be discussed in advance. A phenotypic character is a conventional and unique clinical fact (phenomenon, symptom) related to the patient's morphofunctional characteristic. A phenotypic character should be distinguished from the biological term "phene", which means an individual variant of a certain character and not the presence of the character itself. Also, we won't use the term "stigma", firstly because of its relation to the diagnosed disease, and secondly because of its historical negative accent. Minor development abnormalities (MDA, synonyms: minor malformations or developmental defects, micro anomalies, congenital morphogenetic variants, dysembryogenic stigma, dysgenic or dysplastic characteristics) are minor morphological defects (anatomic abnormality), which are not associated with functional defects of organs and systems. This definition should be supplemented with the presence of the association with the ontogenesis process, persistence [9] and absence of any correlation with age-related features (involution is rare) [10]. A congenital defect (CD) is a congenital abnormality in the organ structure as compared to the anatomic norm, causing clinically significant impairment of its functions [10]. Therefore, a criterion to differentiate between MDA and CD is impaired function. A dysplastic process means a dynamic condition of altered connective tissue exchange, resulting from the interaction between inherited and behavioural factors, environmental conditions and the natural process of growth and ageing of the body. This concept is needed because of the presence of age-related dynamics in connective tissue exchange, which should be taken into account in interpretation of certain EPCs, also when assessing the probability of their natural alternation over time.

The semiotic status of EPC requires clarification; it is definitely symptomatic, i.e. it has a descriptive function. Establishing its association with UCTD as a medical condition or grouping by symptoms requires an additional pathogenetic study with confirmation of laboratory and imaging correlations or statistical associations, grouping these EPCs, which is a partial analysis of the clinical importance of each EPC. Thus, EPC is any unique character irrespective of its nature, inclusion in the organ system or other characteristics, but its clinical interpretation always requires a proof in order to avoid a risk of an accidental mistake.

A study map of phenotypic characters can be diagnostically valuable only with the clear understanding of the methods to establish such characters and strict adherence to such methods by all specialists; otherwise comparability would become challenging. T.I. Kadurina was the first researcher to stress this issue; she established objective criteria for some EPCs directly in the diagnostic chart [6]. For the same reason, phenotypic characters should be analysed in terms of their possible objective definition in the real-time clinical settings.

Each EPC should be analysed together with other clinical presentations because, formally, one phenotypic character can be a part of various clinical conditions — from normal condition or minor abnormality up to a character of a serious inherited pathology (for instance, abnormal ear shape in Beals syndrome patients). Almost all EPCs can be an isolated connective tissue defect in one case and a symptom of a systemic inherited pathology and pleiotropic action of mutant genes in other cases [3, p. 38].

Genetic origin of dysplastic process is out of question; however, we are unable to exhaustively describe pathogenesis of initial elements of EPC, as it can vary due to genetic heterogenity of connective tissue dysplasia, even within a family in inherited disorders [11]. However, we can describe them during or after character formation, because its course corresponds to the anatomical and functional nature of EPC. Therefore, there are two main stages of pathogenesis: before and after EPC formation, including a vicious circle, where this EPC affects dysplastic process.

Nevertheless, some elements of pathogenesis can be assumed on the basis of differential CTDs with known etiopathogenesis, for which this EPC is specific. Thus, a differential CTD is the best model to study pathogenesis of a specific EPC. An affected element in connective tissue can be roughly assumed by the elemental structure of extracellular matrix in affected tissue.

We will use the following plan to study and describe EPC:

1) Classification of a number of various EPCs in order to systematise them and identify groups similar in comparative characteristics.
2) Analysis of each EPC in terms of resulting classification.
3) Description of existing methods to identify these characters; if necessary and possible, proposed adaptation for unification and improvement of diagnostic method significance.
4) Presentation of assumed pathogenesis of these characters based on publications, including with due account to the defective element in connective tissue metabolism and alternative clinical state causes.
5) Assessment of age-related changes in these characters.

Below is a proprietary EPC classification with comments:

1) Association with the organ system [6] — depends on the affected connective tissue location. This comparative character is the most clinically significant, as it defines patient's routing in the clinical network. Besides, understanding of the organ system embryogenesis makes it possible to assume patterns in formation and distribution of subclinical connective tissue defects. Due to its integrative function, connective tissue is present in each and every organ system, including nervous system, and mental disorders are EPC.
2) Method of identification:
   - Objective — can be clearly defined upon subjective examination by a medical professional:
     – Examination (majority of EPCs) — morphological EPCs;
     – Functional test (joint hypermobility, skin hyperextensibility of skin) — functional EPCs;
     + Some EPCs require identification and diagnosis clarification by a medical professional, e.g., scoliosis, flat foot, eye pathology, nasal septum deviation;
   - Subjective — identified as specific senses and feelings by the patient or active complaints;
   - Anamnestic — identified when taking patient's history.

It is also important to differentiate objective characters related to anamnestic data, which can be observed only in specific events, for instance, keloid scars or tissue paper syndrom after a skin damage.

3) Effects on clinical presentation:
   - Clinically significant — affect quality of life and disease outcome;
   - Clinically insignificant — minor development abnormalities.

It is worth nothing that this classification is often relative, because further investigations can bring about actual data on the clinical significance of formed MDAs.

4) Possible character changes:
   - Reversible — can resolve spontaneously over time;
   - Irreversible — can be corrected only with surgery.

This comparative character is a result of morphogenesis, particularly of the rate of connective tissue exchange involved in the formation of this EPC.

5) Incidence:
   - Primary — are common in impaired connective tissue exchange and are highly specific for dysplastic process;
   - Secondary — are less common in impaired connective tissue exchange and are less specific for dysplastic process.
6) Association with ontogenesis:
   - Inherited — the fact and nature of inheritance can be established only following a genealogic analysis (preceding and succeeding generations);
   - Acquired:
     – Congenital;
     – Postnatal.
7) Association with dysplastic process:
   - Cause markers — are a direct cause of impaired connective tissue metabolism, always irreversible;
   - Consequence markers — are a direct consequence of impaired connective tissue metabolism, always reversible;
   - Cause-effect markers — are a direct consequence of impaired connective tissue metabolism, in some way or another they aggravate the process;
   - Associated marker — does not have any direct pathogenetic association with dysplastic process or has unspecified pathogenetic status.

Each of these variants can be of diagnostic importance; however, cause markers are a stronger evidence of CTD, while consequence markers are an evidence of severity.

8) Relation to an effected element of connective tissue:
   - Collagens;
   - Elastin;
   - Glycosaminoglycans (GAGs).

This comparative character is the most pathogenetic, as it describes the mechanism of connective tissue damage in a specific EPC.

Classification based on the relation to the germinal layer has no high diagnostic value, because all connective tissue structures have common mesenchimal origin from the mesodermic layer. Mesenchimal cells form in mesodermal palisades as a result of separation. Further differentiation of the majority of cells in embryogenesis depends on inductive

interaction between epithelial and mesenchimal tissues [12, p. 210]. An alternative understanding is that all germinal layers participate in mesenchyme formation [2, p. 11, 13, p. 16]. Mesenchyme is the totality of loose reticular dendritic cells located bewteen compact cell rudiments (fetal organs). Mesenchyme forms the internal environment for the fetus prior to formation of special integrative systems, and ensures the processes of fetal cell migration, then gives rise to stromal cells (especially for connective tissue, smooth muscle cells), skeletal tissue, vascular system and blood [13, p. 16]. Mesenchyme itself forms during Carnegie stage 6 (week 3): extraembryonic mesenchyme as exoderm thickening in the caudal pole of archiblast, with follow-up lateral cell migration; and intraembryonic mesenchyme resulting from exoderm cell introversion in the germ band area [12, pp. 84–88]. Therefore, the cause of dysplastic process is involvement of a specific cell pool during ontogenesis, specifically in individual or multiple, inherited or newly acquired genetic defects, which can occur at any stage during ontogenesis. It is worth mentioning that other layers are a source of specific epithelia and cells of parenchymatous organs. Skin, teeth, breasts, and nervous system are mostly ectodermic in their origin, while digestive and respiratory systems are mostly enderonic [12, pp. 208, 220, 222, 336]. Knowledge of formation periods of external body parts (face, limbs, etc.) and corresponding internal organs allows suspecting an internal pathology in the presence of EPCs [14].

We will discuss EPCs according to their classifications. Each section contains a common group characteristic, including involved connective tissue elements, and description of individual EPCs; ICD-10 and ICD-11 codes will be provided where available. Groups of craniofacial, wrist and feet characters are grouped on the basis of their anatomical similarity, which is useful for practical diagnostic use. This article discusses only EPCs, which can be identified by GPs. Specialised orthopedic, ophthalmologic and dental EPCs will be discussed in specialised articles. Clinical evaluations were conducted on the basis of a quantitative estimate vs. other EPCs using point-based systems (I.A. Viktorova, L.N. Abbakumova, T.I. Kadurina) or in accordance with the author's interpretation of these characters into primary and secondary (T. Milkovska-Dmitrova and A. Karkashov).

MDAs

This is a separate group; it is the most general and unspecified group, which is a result both of heterogeneity of these EPCs and low awareness of the medical community of this problem [9], thus, the lack of studies and full understanding of the clinical significance MDAs, where several aspects can be distinguished:

1) Isolated MDAs can be observed in healthy individuals [9, 15].
2) Multiple MDAs are clinically significant, quantification of which in publications varies between 3 and 7 [15]:
   - Accumulation of MDAs in several generations as a sign of dysplastic stigmatization [10];
   - Risk stratification for the inherited pathology for detailed diagnosis and family planning [9];
   - Risk stratification for hidden CDs for detailed diagnosis [15];
   - Indications for common preventive measures [9].
3) Clinically significant is a combination of MDA and CD, which indicates unconditionally abnormal nature of MDA [9].
4) Clinically significant is a combination of specific MDAs, for instance, transverse palmar crease, upslanting palpebral fissures, epicanthal fold, brachydactylia, clinodactyly, sandal gap in Down syndrome [14].
5) Clinically significant are specific MDAs, for instance alar neck folds (Turner syndrome and Noonan's syndrome), postaxial polydactyly (Bardet-Biedl syndrome), breast nipple hypoplasia or aplasia on one side (Poland's syndrome), vertical notches on the ear lobe (Beckwith-Wiedemann syndrome) [14].

Therefore, MDAs are just a sign of antenatal ill-being irrespective of the causative factor, including inheritance. There is a proven correlation between MDA incidence and anthropometric characteristics within the population and the ecological conditions in the location of early development [16], aggravated obstetric and gynecological history (number of pregnancies, mother's age, mother's drug addiction, premature birth) [17, 18]. In a clinical and genealogic analysis, inherited nature of feet and hand MDAs are observed only in one quarter of all cases [19]. Over 50 % of all MDAs have a composite origin [20].

The terms "norm", "MDA", "CD", and "EPC" should be defined here. The most close concepts are MDA and CD, which have common morphological nature and are associated with impaired ontogenesis. They are caused by similar factors; however, the causative factor differs in intensity, exposure duration and period of fetal exposure (critical or non-critical development stages) [9]. Abnormality is a condition beyond variations or borderline changes in the normal condition [15]. The correlation between MDA and EPC is more complicated. In general, MDAs are associated with dysplastic process, that is why a direct pathogenetic correlation with it is doubtful, but possible, it being proven by the traditional use of MDA in diagnosting connective tissue

dysplasia [10, Table 1] due to a high incidence of MDAs in UCTD, but this topic requires additional studies for each specific MDA. The association is a result of the shared causative factors of MDA and connective tissue displasia. In this regard, it is not a surprise that articles by Russian authors on MDAs were in the area of neurology [9] and orthopedics [21], i.e. fields of medicine, which study pathologies of the systems, where connective tissue prevails. Of note, all MDAs are EPCs, and just some morphological EPCs are MDAs. The majority of MDAs tend to progress before puberty ends, then the process stops together with growth of the body.

Anamnestic and subjective EPCs

This EPC group is the most polygenic one, therefore, in order to establish its association with dysplastic process, other causes should be ruled out (idiopathic nature of disorders), and very often it is a very time-consuming process, which requires additional diagnostic and medical resources.

The group of anamnestic characters (Table 1) can be classified as follows:

- No signs upon examination; however, they can be retrospectively recovered by the patient (e.g., easy bruising).
- Diagnoses made by a medical professional (eye specialist, trauma orthopaedist, dentist), also on the basis of additional examination techniques (laboratory tests, imaging).
- Prior diagnoses, which were not observed upon examination as they were corrected (e.g., hernias in any location).

This group of characters includes mostly symptoms of hemostasis pathology, impaired sexual maturation, and a history of traumas.

In terms of diagnostic informative value, this group is inferior to objective characters, because diagnosis depends on the possibility to compare with normal values under similar conditions. Connective tissue dysplasia has a huge impact on the quality of patient's life, so that they are in completely different settings, where internal differences can be left hidden. The patient will be living with impaired functionality and anamnestic EPCs will emerge only under a stress as dysplastic process decompensation or in a specific life style, e.g., in sportsmen. Besides, these characters are somehow subjective, which is a result of both the patient's psychological constitution, where existing EPCs can be disregarded or left out altogether, and unclear incidence and intensity (lack of clear criteria). Also, this group of characters is greatly impacted by the healthcare service availability, because in the absence of comprehensive examinations and consultations by medical professionals, which is the case with minor changes, these EPCs will be disregarded, while their identification by a non-competent GP will lead to diagnosis subjectification and possible overdiagnosis. Therefore, this group of EPCs reflects not only internal features of the patient's health, but also external factors of the patient's life style, quality of healthcare services and patient's psychological constitution.

Out of a wide group of subjective characters observed in UCTD, only a few complaints, which are specific to dysplastic process and related to joint disorders, are used in the diagnosis (Table 2).

Table 1. *Anamnestic EPF*

EPF	Clinical assessment	ICD-10 and ICD-11 codes
Petechiae/ecchymosis/nosebleeds	Kadurina T.I. — medium	Other specified hemorrhagic conditions D69.8, 3B6Y
Easy occurrence of hematomas	Abbakumova L.N. — medium	Other specified coagulation disorders D68.8, 3B6Y
Juvenile uterine bleeding	Kadurina T.I. — small	Heavy menstruation during puberty N92.2, other specified abnormal bleeding from the uterus and vagina N93.8, GA2Y
Delayed puberty	Kadurina T.I. — small	Delayed puberty E30.0, 5A91
Dislocations and subluxations in joints or only dislocations	Milkovska-Dmitrova T. and Karkashov A. — secondary Viktorova I.A. — medium	Recurrent dislocations and subluxations of the joint M24.4, bone dysplasia with multiple dislocations of the joints LD24.E, the specified code depends on the location and is assigned by an orthopedic traumatologist
Varicose veins of the lower extremities, vulva, and pelvis in young adults	Not defined	varicose veins of lower extremities without ulcer or inflammation I83.9, Chronic venous Insufficiency of lower extremities BD74, Varicose veins of vulva BD75.2, Varicose veins of pelvis BD75.3
Hernias and prolapses of pelvic organs and/or postoperative hernias, diaphragmatic hernia	Not defined	Prolapse of female genital organs N81, hernia of the anterior abdominal wall K43, DD55, diaphragmatic hernia K44, DD50.0
Bone fragility — more than 2 fractures in history from falls	Not defined	Osteogenesis imperfecta Q78.0, congenital bone fragility LD24.K0
Hearing loss, deafness	Not defined	Unspecified hearing loss H91.9, deafness AB5Z

Table 2. *Subjective EPF*

EPF	Clinical assessment	ICD-10 and ICD-11 codes
Pain in the spine	Kadurina T.I. — medium	Back pain — M54, ME84
Arthralgia/microtraumatic transient synovitis or transient joint pain	Kadurina T.I. — medium or Milkovska-Dmitrova T. and Karkashov A. — secondary	Joint effusion — M25.4, Transitional synovitis — FA27.3 Joint pain — M25.5, ME92

However, these symptoms can be a consequence of other pathologies — rheumatological, traumatological, orthopaedical, infectious or metabolic pathologies. The specificity of these complaints can be boosted due to clarification of the clinical presentation and history; however, the specificity is unclear. UCTD patients are known to have numerous complaints, resulting from a low pain threshold and specific psychological profile.

Bone EPCs

The majority of bone EPCs are specific orthopaedical characters (deformed chest, spine and limbs, bone and cartilage dysplasias) and dental characters (high archlike palate, impaired tooth growth and density). GPs can use a measuring tape for measurements and calculate bone indices in order to identify constitution and individual disproportions. Given limitations of a measuring tape, it is essential to use values, which minimise the impact of muscles on measurement results; a sliding caliper will help in eliminating these limitations.

Bone characters have the highest sensitivity and specificity for clinical diagnosis of UCTD, since they are the least age-related (save for spine and foot deformities).

The connective part of a (demineralised) bone contains 90 % of type I collagen, 1–2 % of type V collagen, 2–3 % of osteonectin, and 1 % of proteoglycans, sialoproteins, osteocalcin, and α2-glucoprotein each.

Differential CTDs associated with the most pronounced changes in bones are Marfan's syndrome and brittle bone disease.

Dolichostenomelia (Q74.8 "Other specified congenital malformations of limb(s)", I.A. Viktorova — minor, T.I. Kadurina — moderate). According to the meaning of the components of this term: "dolichos" is long, "stenos" is narrow, and "melos" is a part of the body, limb, the term means elongation and thinning of limbs. This condition has clear clinical global signs for estimated indices; both must be present [22]:

- The ratio between the upper body (from the top of the head to upper symphysis) and the lower body (from upper symphysis to the floor) is < 0.86.
- The ratio between arm span and height is ≥ 1.05.

There are also additional characters [2, p. 45]:

- The ratio between feet length and height is > 15 %.
- The ratio between hand length and height is > 11 %.
- The difference between arm span and height is > 7 cm.

Bone and cartilage dysplasiae (same code) are bone structure abnormalities caused by impaired histogenesis; the clinical evaluation is unspecified [2, p. 48]:

- Acromelia is associated with shortening of distal limb sections (hands, feet);
- Mesomelia manifests as shortening of central limb sections (forearm, shin);
- Rhizomelia is shortening of proximal limb sections (shoulder, hip).

Identification is based on the measurements of limb section length and calculation of the ratios between section length and limb length; the resulting values are also compared to the normal values.

Restricted elbow extension of ≤ 170 degrees (ICD is not available) — the clinical evaluation is unspecified [22]. It is measured as part of goniometry.

Elbow extension is controlled by three factors: flexor muscle resistance (biceps, brachialis, brachioradial muscle), anterior joint capsule tension, and crazy bone contact with cubital fossa [23, p. 98]. Therefore, restricted extension is caused by disproportional crazy bone enlargement as compared to cubital fossa.

Skin EPCs

In its composition, the connective tissue part of the skin, comprising mostly the proper dermal layer, is similar to ligaments and tendons. Since skin is able to renew tissues faster, first, skin EPCs are most susceptible to age-related changes; second, they are very sensitive to changes in the current connective tissue metabolism.

All EPCs, participating in the diagnostic process, should be identified on a specific, pre-defined standard skin area, which is hardly exposed to external factors (native skin), primarily to mechanical load and solar irradiation, and which shows innate characteristics of the individual and not the features of their environment. The interscapular region is optimal, because it is covered with clothes most of the time.

It is worth noting that this group has a large number and some analogy-based metaphoricity in EPC terminology; however, the majority of them can be grouped together based on the affinity of the described skin characteristics.

We believe that the key characteristics are skin stretchability, surface condition, consistence, and elasticity; however, the main characteristic is consistency, as it affects the majority of the all other qualities. Soft skin is most likely stretchable and velvety (T.I. Kadurina — minor), while dense skin would be poorly stretchable and smooth. In terms of the connective tissue element, this characteristic is based on the collagenous matrix quality, in particular its architectonics parameters: in case of a poor structure, even de-fragmentation, more space would be required to line up individual fibres along the mechanical power application line during stretching; clinically, it means high stretchability. The surface section of this matrix will be also altered, it will have fine irregularities, showing as velvety skin. A characteristic, which is close to consistence, is tissue tension (the ability of soft tissue, particularly skin, to mechanically resist external exposure), which also depends on the rate of hydration [24].

Skin elasticity is the ability of skin to recover its shape after removal of deforming load. This quality depends on the elastic component of connective tissue. To sum up, skin is streched due to mechanical properties of the collagenous matrix, and skin shape is recovered due to the elastic matrix. Each of the discussed clinical properties of skin is self-sufficient and, to a great extent, depends on a specific element of connective tissue.

Some skin EPCs are palpable (tactile characteristics and functional tests) and some can be seen upon examination (visual properties). Tactile characteristics are surface condition (stroking), consistence (pinching with tissue compression), elasticity (pinching, but removal of compression), and stretchability (pulling).

Consistence can be soft (loose) or dense. Skin surface can be velvety or smooth; these are alternative, mutually exclusive characteristics. Velvet has thick fluff, giving the fabric specific tactile properties. Velvety skin means the degree of skin humidity, which, in turn, depends on the degree of hyaluronic acid and water in skin matrix. Two different connective tissue elements impact one skin property, because both collagenic fibrils and GAG take part in derma frame formation [25, p. 31]. In children, velvety skin can be a result of abundance of lanugo hairs; however, this mechanism is possible in adult patients with UCTD (lanugo hairs of various length). The synonym of this characteristic is chamois-like skin (L.N. Abbakumova — minor), because one of the stages in chamois preparation is fluffing, similar to teaseling, giving it similar tactile properties; and delicate skin (T.I. Kadurina — minor).

In terms of elasticity, skin can have decreased elasticity (synonyms: fragile, loose skin (I.A. Viktorova — moderate), which swags by gravity) and normal elasticity (synonyms: elastic, resilient, firm skin). In terms of stretchability, skin can have decreased (rigid skin), normal and increased (ropy skin) stretchability ; however, this characteristic should be assessed quantitatively.

Increased stretchability (hyperextensibility, not hyperlaxity) (other specified disorders of skin and subcutaneous tissue in diseases classified elsewhere (Ehlers-Danlos syndrome), L99.8, M.J. Glesby, T. Milkovska-Dmitrova and A. Karkashov + “flappy” — primary, L.N. Abbakumova — moderate, I.A. Viktorova — major, T.I. Kadurina — moderate to major).

There are several methods to determine skin stretchability, but they are based on pulling, which can be criticised because of the challenges with this procedure standartisation, which requires clarification of the following questions: Which skin area? (potential impact from peculiar interface between skin and subcutaneous tissue) What skin area to be gripped? How to grip skin relatively to skin strain lines? What pulling force to apply to the skin fold? What point and what side of the skin fold to use for fold length measurements? None of the methods answers these questions. In Russia, we mostly use measurements of hyperextensibility of skin on the dorsum of hand, halfway through the projection of the 3rd metacarpal bone; the fold is formed in parallel with this bone. Alternatively, skin of the forehead or above outer ends of the clavicle can be used [26]. Assessment criteria also differ: increased skin stretchability means skin fold length of 2–3 cm and above. Degree of stretchability can be measured: minor — up to 2 cm, moderate — up to 3 cm, and severe — 4 cm and over [6]. The binary version of this characteristic can be assessed as well, where hyperextensibility means the possibility of forming a skin fold at the nose tip or external ear. The force applied should not cause any pain. Foreign publications recommend studying a skin fold at the upper third of the palmar surface of forearm laterally [27, 28].

An adequate alternative is stretching on a surface between two standard lines (2 cm apart) at the upper third of the palmar surface of forearm laterally, as it allows preventing all mentioned limitations of the methods, which are based on the use of a skin fold. The force applied is limited by a sudden rise in skin resistance to stretching; this is a moment, when collagenous matrix lies along mechanical strain lines.

Another group of affinity is thin skin (T.I. Kadurina — moderate, I.A. Viktorova + “translucent skin” — minor), which is sometimes called fragile (strength characteristic). This EPC also includes visible venous or vascular pattern of skin (synonym: vascularity) (L.N. Abbakumova — moderate, T. Milkovska-Dmitrova and A. Karkashov — primary), because this visual

feature is used to clinically identify skin thinning. Examinations are conducted on skin of chest and back, limbs are used less often. It is also suggested to identify dilated capillaries of skin on face and back (L.N. Abbakumova — minor). Tool-based methods can be used, e.g., anthropologic invasive skin thickness gage and ultrasound cutometry. There are specialised combined diagnostic equipment used in dermatology, which is the golden standard in the measurements of the majority of skin parameters [29], and dermatological ultrasound examination [30].

A separate group is skin changes associated with traumas and/or active growth (teenagers, pregnant women, sportsmen, obese people). After a trauma, when skin heals, there can be skin areas resembling tissue paper (I.A. Viktorova — moderate, T.I. Kadurina — minor to moderate, depending on the size), which look like wide atrophic (below skin level, shiny) scars with multiple folds, resembling crumpled up paper. Usually, it is possible to retrospectively identify the fact of a non-linear trauma (abrasion, impact injury) or past infections with skin involvement (streptoderma, chicken pox, etc.). We believe that a higher clinical value lies not with the size or number of these EPCs, which, to a greater extent, are related to the nature of trauma and its probability, but the very fact of this type of skin regeneration. A similar mechanism underlies formation of stretch marks (L90.6, EE40.1) in rapid growth areas (breast, buttocks, shoulders during puberty, abdomen in pregnant women or obese people), which are also atrophic scars, but are numerous and linear (I.A. Viktorova — minor, T.I. Kadurina — major). It is recommended to evaluate them in posterolateral areas of chest, at the level of inferior thoracic segment and lumbar spine section [6]. The colour of strech marks does not have any clinical significance and only shows their age (discoloration over time). A synonym of this EPC is skin scarring (L.N. Abbakumova — minor).

Another type of pathological skin healing is keloid scars, when the poor fibril quality is compensated with their amount, and a hypertrophic scar with impaired structure is formed (L91.0, EE60.0), T.I. Kadurina — minor to moderate, depending on the number. Such scars can appear in the area of any trauma, including surgery and vaccination sites, and require targeted history taking in order to know where to look for them.

Consistence is directly associated with EPC multiple pigment spots, skin hyperpigmentation (unspecified disorder of pigmentation L81.9, abnormal skin pigmentation ED64), M.J. Glesby, L.N. Abbakumova — minor, T.I. Kadurina — moderate. Since soft skin is well-stretchable near natural bony prominences, for instance, above spinous processes of thoracolumbar vertebrae, there are conditions for mechanical stimulation of melanine deposits in these areas. Over 20 such deposits means they are multiple.

Skin colour depends on microcirculation condition, which is impacted by its vegetative regulation and overall pigmentation, which in clinical settings can be assessed using phototypes in Fitzpatrick scale. UCTD patients are pale (L.N. Abbakumova — minor), which is a sign of sympathicotonia.

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Информация об авторах

Котовщикова Елена Фёдоровна — доктор медицинских наук, профессор, заведующая кафедрой пропедевтики внутренних болезней имени проф. З.С. Баркагана, ФГБОУ ВО «Алтайский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Барнаул, e-mail: kotov-l@mail.ru, ORCID ID: https://orcid.org/0000-0002-3246-5609

Сидоровъ Николай Сергиевич — аспирант, ассистент кафедры пропедевтики внутренних болезней имени проф. З.С. Баркагана, ФГБОУ ВО «Алтайский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Барнаул, e-mail: meinweg@yandex.ru, ORCID ID: https://orcid.org/0000-0003-3890-6855

Author information

Elena F. Kotovshchikova — doctor of medical sciences, professor, head of the department of propaedeutics of internal diseases named after professor Z.S. Barkagan, Altai State Medical University, Barnaul, e-mail: kotov-l@mail.ru, ORCID ID: https://orcid.org/0000-0002-3246-5609

Nikolay S. Sidorov' — postgraduate student, assistant of the department of propaedeutics of internal diseases named after professor Z.S. Barkagan, Altai State Medical University, Barnaul, e-mail: meinweg@yandex.ru, ORCID ID: https://orcid.org/0000-0003-3890-6855

Автор, ответственный за переписку / Corresponding author