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NEUROLOGICAL CHANGES AND DIAGNOSTIC EVALUATION ALGORITHM IN UNDIFFERENTIATED CONNECTIVE TISSUE DYSPLASIA

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Abstract: Undifferentiated connective tissue dysplasia (UCTD) is a heterogeneous group of disorders characterized by pathological changes in various organs and systems. Despite its widespread occurrence, the clinical manifestations - particularly neurological changes - remain insufficiently studied. This article analyzes the clinical features, pathogenetic mechanisms, and diagnostic approaches to neurological disorders in patients with UCTD.

Keywords: Undifferentiated connective tissue dysplasia, collagen and elastin disorders, neurological changes, autonomic dysfunction, genetic factors, diagnostics.

Introduction

Undifferentiated connective tissue dysplasia (UCTD) represents a heterogeneous group of disorders characterized by morphological and functional abnormalities. These alterations affect multiple organs and systems, including the musculoskeletal, cardiovascular, and nervous systems [1].

Neurological aspects are of special interest since connective tissue plays an important role in maintaining the structural and functional integrity of the peripheral nervous system, vascular network, and the brain and spinal cord [2].

The aim of this paper is to systematically analyze neurological symptoms, their pathogenetic mechanisms, and diagnostic approaches in UCTD.

Main Part

Undifferentiated connective tissue dysplasia (UCTD) is a hereditary, multisystem disorder characterized by polymorphic clinical manifestations resulting from genetic defects in connective tissue structure and function [1,3,4]. It is termed “undifferentiated” because no specific gene mutation or syndrome (such as Marfan or Ehlers–Danlos) can be identified, although weakness, elasticity, and reduced strength of connective tissue are evident [2].

UCTD arises from hereditary and molecular defects in the synthesis, assembly, or degradation of collagen, elastin, fibrillin, and other connective tissue components. It affects various systems (skeletal, cardiovascular, nervous, skin, visual, and genitourinary).

Unlike defined syndromes such as Marfan, Ehlers–Danlos, or Loeys–Dietz, UCTD lacks a specific molecular identifier.

Classification is based on clinical criteria [4]:

By symptom severity: mild, moderate, severe

By predominant system involvement: cardiovascular, skeletal, neurological

By age of manifestation: childhood, adolescence, adulthood [3].

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In the literature, multisystemic forms of UCTD are often highlighted, where neurological symptoms may appear early and be dominant.

Pathogenetic Mechanisms of Neurological Disorders in UCTD

1. Structural connective tissue abnormalities – Genetic defects in collagen and elastin synthesis reduce the stability of nerve tissue and surrounding structures, leading to joint hypermobility, spinal instability, nerve root compression, and chronic pain syndromes [5].

2. Microcirculatory disturbances – Due to vascular wall fragility, nerve tissues receive insufficient oxygenation, resulting in decreased functional activity and peripheral neuropathies [6].

3. Mechanical factors – Spinal and joint instability may cause mechanical compression of nerve roots, leading to radiculopathies and muscle-tonic syndromes [7].

4. Autonomic nervous system dysfunction – Impaired autonomic regulation results in changes in heart rate, hypotension, abnormal sweating, and overall vegetative lability [8,9].

Modern research shows that the combination of genetic connective tissue defects and secondary mechanical stress produces a wide spectrum of neurological symptoms [9].

Neurological Manifestations of UCTD

The severity of neurological symptoms depends on the disease form and may include:

Headache and migraine, often related to vascular tone instability and altered reactivity to pressure changes [8].

Nerve root compression with pain, paresthesia, and limb weakness.

Autonomic dysfunction such as orthostatic hypotension, tachycardia, sweating disturbances, and emotional instability [10].

Motor and coordination disorders related to spinal instability and peripheral nerve involvement; muscle weakness, imbalance, dizziness, and fatigue are common.

In many cases, neurological signs are the first manifestations of UCTD and require clinical assessment and diagnosis.

Diagnostics of UCTD

UCTD diagnosis is complex, requiring the integration of clinical, morphological, instrumental, and laboratory data since no specific genetic markers are typically identified.

1. Clinical Diagnosis

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The foundation of UCTD diagnosis lies in phenotypic assessment and comprehensive clinical evaluation.

1.1. Clinical Criteria

The most common features include:

Joint hypermobility (Beighton score ≥ 5)

Muscle hypotonia

Spinal deformities (scoliosis, kyphosis, lordosis)

Skin hyperextensibility and thinness

Cardiovascular abnormalities (mitral valve prolapse, aortic dilatation)

Cervical or spinal instability

Fatigue, headache, dizziness, autonomic instability

These are evaluated using the phenotyping tables developed by Kadurina T.I. and Gorbunova V.N. (2009), where each symptom is scored to determine the likelihood of UCTD.

1.2. Neurological Examination

Neurological manifestations often appear early; therefore, assessment includes:

Muscle strength and tone

Coordination (Romberg, finger-to-nose test)

Sensitivity (paresthesia, hyperesthesia, hypoesthesia)

Reflexes (tendon and pathological)

Autonomic signs (orthostatic hypotension, tachycardia, HR variability) [11].

2. Instrumental Diagnostics

Instrumental studies play a key role in confirming systemic involvement.

2.1. X-ray and MRI

Detect spinal instability, scoliosis, or dysplastic changes

Identify herniated discs and nerve compression

Assess for meningeal prolapse, syringomyelia, or Arnold–Chiari malformation

2.2. Echocardiography (ECHO)

Evaluates valve prolapse, aortic dilatation, and cardiac wall abnormalities

2.3. Doppler Ultrasound (USDG)

Measures cerebral and cervical blood flow, vasospasm, or stenosis

Demonstrates hemodynamic changes due to autonomic dysfunction

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2.4. EEG

Records bioelectrical activity in the brain and is used in cases of migraine, headache, or autonomic instability [12].

3. Laboratory and Genetic Diagnostics

Molecular confirmation is challenging due to the absence of specific gene mutations, yet biochemical tests can be informative.

3.1. Biochemical Indicators

Hydroxyproline levels – reflect collagen breakdown

Oxyproline/creatinine ratio – indicates collagen turnover activity

Elastin and fibrillin markers (ELN, FBN1 gene products) – assess dysplasia severity [13].

3.2. Genetic Testing

Mutations in genes related to collagen synthesis (COL1A1, COL3A1, COL5A1, etc.) can be found but are often uncertain or heterozygous.

Thus, genetic testing serves as a supportive, not a primary, diagnostic tool.

4. Systemic (Integral) Diagnostics

A comprehensive, multidisciplinary evaluation is essential [14]:

Assessment by rheumatologist, neurologist, cardiologist, orthopedist, and ophthalmologist

Phenotypic scoring for each system (e.g., heart – 3 points, nervous system – 2 points, skeletal – 2 points)

The total score determines disease severity (mild, moderate, severe)

Comprehensive diagnostics help differentiate UCTD from other hereditary connective tissue syndromes and establish prognosis.

Conclusion

Neurological aspects of undifferentiated connective tissue dysplasia play a significant role in the clinical picture. Early diagnosis, systematic evaluation of nervous system involvement, and integrated treatment approaches reduce the risk of complications and improve prognosis.

Future studies should focus on elucidating pathogenetic mechanisms and developing targeted therapeutic strategies.

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