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Case series

Multiple malformations due to dysplastic changes in connective tissue in children

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ABSTRACT

BACKGROUND: Connective Tissue Dysplasia (CTD) in pediatric populations represents a heterogeneous group of heritable disorders characterized by structural and functional anomalies in connective tissues, primarily involving abnormalities in collagen, elastin, and other essential extracellular matrix components. These anomalies manifest through a spectrum of clinical phenotypes affecting multiple organ systems. This study aimed to investigate lesser-known systemic lesions in children with dysplastic changes in connective tissue to enable timely diagnosis and comprehensive treatment.

CASE PRESENTATION: Clinical Case 1: A 15-year-old boy presented with recurrent bronchitis, pneumonia with obstructive syndrome, and asthma attacks. Allergological examination revealed significant increases in total Immunoglobulin E (IgE). Computed Tomography (CT) scans showed fibrous cortical defects and severe osteoporosis in various bones. The clinical diagnosis included undifferentiated CTD syndrome, joint hypermobility syndrome, and multiple fibrous cortical defects, among other conditions. Clinical Case 2: A 15-year-old girl with bilateral flat feet, increased thoracic kyphosis, and leftward spinal axis deviation was diagnosed with joint hypermobility syndrome. An incidental finding of a large cyst in the lower pole of the spleen was surgically treated.

CONCLUSION: Dysplastic changes in connective tissue present through various clinical conditions, highlighting the need for a comprehensive examination. The combination of undifferentiated CTD with fibrous cortical defects, osteochondropathy, cystic changes in internal organs, and other developmental anomalies underscores the need for further in-depth research.

KEYWORDS: Connective Tissue Dysplasia; pediatric; fibrous cortical defects; joint hypermobility syndrome; osteochondropathy; cystic changes; comprehensive examination.

INTRODUCTION

Connective Tissue Dysplasia (CTD) in pediatric populations represents a heterogeneous group of heritable disorders characterized by structural and functional anomalies in connective tissues, primarily involving abnormalities in collagen, elastin, and other essential extracellular matrix components.[1] These anomalies manifest through a range of clinical phenotypes affecting multiple organ systems.[2] The pathogenesis of CTD often involves mutations in genes encoding fibrillin-1 (FBN1), collagen (COL1A1, COL1A2), and other structural proteins critical for connective tissue integrity and elasticity.[3] Cardiac involvement in CTD is commonly observed, including valvular pathologies such as mitral valve prolapse (MVP), aortic root dilation, and aneurysms.[4] These conditions can lead to hemodynamic alterations, requiring echocardiographic monitoring and, in some cases, prophylactic surgical intervention. The presence of vascular anomalies, such as varicose veins, arteriovenous malformations, and spontaneous dissections, further complicates the clinical course.[5,6] Skeletal manifestations of CTD include generalized ligamentous laxity, predisposition to joint hypermobility syndrome (JHS), and recurrent dislocations. Thoracic deformities like scoliosis and pectus excavatum are common, while orthopedic anomalies include pes planus

(flatfoot) and syndactyly (fusion of digits).[7,8] Musculoskeletal pain and fatigue are prevalent, often necessitating interdisciplinary management involving physiotherapy and orthopedic support.[9,10]

Visceral complications arise from inherent connective tissue fragility, leading to conditions such as nephroptosis (renal ptosis), gastroptosis, and various forms of herniation, including hiatal hernia.[11] Gastrointestinal manifestations, such as esophageal dysmotility, esophageal diverticulum, and gastroesophageal reflux disease (GERD), warrant endoscopic evaluation and, if necessary, surgical correction. Genitourinary involvement, particularly pelvic organ prolapse in females, requires gynecological assessment and intervention.[12] Ophthalmological findings in CTD may include high myopia, astigmatism, and lens dislocation (ectopia lentis).[13] Retinal detachment and other vitreoretinal pathologies necessitate regular ophthalmologic monitoring and potential surgical repair. Strabismus and amblyopia are additional ocular morbidities observed in this patient group.[14] The diagnosis of CTD involves a multidisciplinary approach, including detailed family history, genetic testing (e.g., sequencing of FBN1, COL1A1/2), and comprehensive clinical evaluation. Radiographic imaging, such as Magnetic Resonance Imaging (MRI) and Computed Tomography (CT), helps delineate anatomical abnormalities, while echocardiography is essential for cardiac assessment and orthopedic evaluations ensure musculoskeletal integrity.[15,16]

Therapeutic strategies for CTD are primarily supportive and symptomatic. Beta-blockers and angiotensin receptor blockers (ARBs) may be used to mitigate aortic dilation. Orthopedic interventions can range from bracing to corrective surgeries, while physical therapy focuses on enhancing joint stability and muscle strength. Ophthalmologic and gastrointestinal management is tailored to specific manifestations, with surgical interventions reserved for refractory cases.[17] The prognosis of pediatric CTD varies depending on the severity and extent of organ involvement.[18,19] Early detection and a tailored, multidisciplinary treatment regimen are essential for optimizing clinical outcomes and improving quality of life. Phenotypic variability in CTD is influenced by the type and location of genetic mutations, leading to diverse clinical presentations. For instance, Marfan Syndrome, often associated with mutations in the FBN1 gene, is characterized by systemic involvement, including cardiovascular, ocular, and skeletal manifestations.[3,20] Ehlers-Danlos Syndrome (EDS), which includes multiple subtypes such as classical, hypermobile, and vascular forms, is linked to mutations in various collagen genes (COL5A1, COL5A2, COL3A1) and exhibits a broad range of tissue fragility and hyperextensibility.[21]

Emerging research has highlighted the role of microfibril-associated glycoproteins (MAGPs) and small leucine-rich proteoglycans (SLRPs) in the pathogenesis of CTD.[22] These molecules are integral to the structural integrity and function of the extracellular matrix, and their dysregulation contributes to the phenotypic features observed in CTD.[23] Advanced genetic testing techniques, such as whole-exome sequencing (WES) and next-generation sequencing (NGS), have facilitated the identification of novel genetic variants and enhanced our understanding of the molecular underpinnings of CTD.[24] Recent advances in imaging modalities, including 3D echocardiography and cardiac MRI, have improved diagnostic accuracy for detecting aortic root dilation and valvular abnormalities.[25] These tools are crucial for early intervention and monitoring disease progression in children with CTD. Additionally, elastography, an imaging technique that measures tissue stiffness, is being explored as a potential non-invasive method for assessing the biomechanical properties of connective tissues in vivo. The management of CTD has incorporated novel therapeutic approaches aimed at targeting the underlying molecular pathways. For example, losartan, an angiotensin II receptor blocker, has shown promise in reducing aortic dilation in Marfan Syndrome by modulating the TGF-β signaling pathway. Furthermore, enzyme replacement therapy (ERT) and gene therapy are being investigated for certain subtypes of EDS, offering potential disease-modifying treatments.[26]

Physical activity and lifestyle modifications play a crucial role in the management of CTD.[27] While high-impact sports and activities that place excessive strain on the joints are generally discouraged, low-impact exercises such as swimming and cycling are recommended to maintain cardiovascular fitness and muscle strength. Tailored physiotherapy programs, emphasizing joint stabilization and proprioceptive training, can help mitigate the risk of dislocations and improve overall functional outcomes.[28] Psychosocial support is also a vital component of comprehensive care for children with CTD. The chronic nature of the condition, along

with potential physical limitations and visible deformities, can affect mental health and quality of life. Multidisciplinary teams, including psychologists and social workers, are essential in providing holistic care that addresses both the physical and emotional needs of affected individuals and their families.[22] CTD in children encompasses a broad spectrum of genetic disorders with multisystem involvement.[29] Advances in genetic research, diagnostic imaging, and therapeutic strategies have greatly improved our ability to diagnose and manage these complex conditions. Ongoing research and a multidisciplinary approach are crucial for optimizing outcomes and enhancing the quality of life for children with CTD.

The purpose of the study was to investigate the lesser-known systemic manifestations of CTD in children, with the aim of ensuring timely diagnosis and comprehensive treatment of these pathological abnormalities.

CASE PRESENTATION

Children undergoing inpatient treatment were examined, and two clinical cases with multiple malformations were presented. A thorough study of the patients' medical histories was carried out, including conversations with the parents, and detailed information about the patients was collected. Inpatient and outpatient records were examined. All necessary approvals were obtained, and there was no conflict of interest. The data obtained were compared with the results of research conducted by scientists over the past ten years. A comprehensive examination was carried out, including radiography (standard equipment), ultrasound (MEDISON SA-800EX sonograph, Siemens Acuson X-300), CT (PHILIPS Brilliance CT 64), plantography, enzyme-linked immunosorbent assay (quantification of total IgE) (Table 1), and allergy tests.

Table 1. Indicators of total immunoglobulin E.

Indicator	Obtained result		Age norm
Immunoglobulin E total (Ig E)	2009	1005,0 IU/ml	1-5 years 10-50 IU/ml
	March 2018	1060,0 IU/ml	5-15 years 16-60 IU/ml
	April 2018	1164,0 IU/ml	5-15 years 16-60 IU/ml
	2020	1546,0 IU/ml	5-15 years 16-60 IU/ml
	2023	902,49 IU/ml	5-15 years 16-60 IU/ml

Clinical case 1

A boy, P., aged 15 years, was born from the second full-term pregnancy, mixed breech presentation, via caesarean section, with a birth weight of 3400 g. Since early childhood, he has suffered from recurrent bronchitis and pneumonia with obstructive syndrome. Later, he developed attacks of suffocation 1-2 times a month. He has been repeatedly treated in hospitals and outpatient clinics, with his choking attacks relieved by inhalation of Berodual, and he has been using Singulair for a year. The last choking attack occurred three days before admission.

The patient's allergic history was complex. An allergological evaluation identified the following household allergens: Cladosporium (+), pillow feathers (+), and grass dust (+). The house dust was enriched with Dermatophagoides pteronyssinus (++), farine (+), and acarus (+). Epidermal allergens included cat hair (+) and sheep hair (+). Pollen allergens identified were dandelion (+), fescue (+), fireweed (+), and timothy (+). A dynamic enzyme-linked immunosorbent assay showed a significant increase in total IgE (see Table 1).

A CT scan of the knee joints revealed a change in the bone structure of the left femur along the medial surface of the distal metaphysis in a linear shape, presenting as a cortical defect not exceeding its thickness, with clear sclerotic contours and no condyle reaction (Figure 1A). Similar bone changes were found on the medial surface of the proximal metaphysis of both tibiae, showing foci of osteolysis with clear edges, oriented along the bone axis. In some places, the cortical layer is sharply thinned or not visible. There is no reaction of the periosteum and soft tissues (Figure 1B). The apophysis of the left tibia is thickened and fragmented with severe osteoporosis (Figure 1C).

The condition of the feet and the degree of flattening of the longitudinal and transverse arches were assessed using the most common method, plantography (a graphic impression of the plantar surface of the feet). A

clinical diagnosis was made: undifferentiated CTD syndrome, JHS, multiple fibrous cortical defects of the proximal tibial metaphysis and distal metaphysis of the left femur, left-sided Osgood-Schlatter disease, bilateral flat feet, scoliotic posture, anterior chest wall development anomaly, left varicocele (Figure 2A), curvature of the nasal septum, multiple caries, transverse chord of the left ventricle, bronchial asthma (atopic form, intermittent course), allergic rhinitis, and hypertrophy of the nasopharyngeal tonsils.

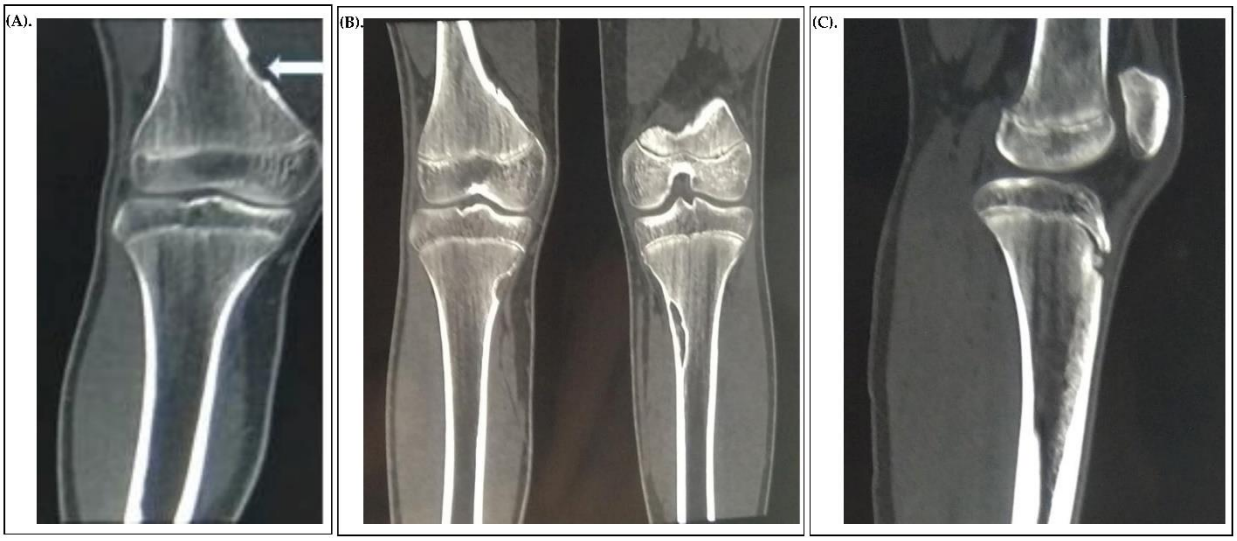

Figure 1. Radiological findings of the patients. (A) Patient P, 15 years old, CT scan of the lower leg showing a fibrous cortical defect of the distal metaphysis of the left femur. (B) Patient P, 15 years old, CT scan of the lower leg showing a fibrous cortical defect of the distal metaphysis of the left femur. (C) Patient P, 15 years old, CT scan of the lower leg showing osteoporosis and fragmentation of the apophysis of the left tibia (Osgood-Schlatter disease).

Clinical case 2

Girl P., 15 years old, consulted an orthopedist with complaints of flattening of both feet. She was born from the second full-term pregnancy via normal delivery, with a birth weight of 3800 g. She was breastfed for up to a year and grew and developed normally. Examination revealed pronounced flattening of the longitudinal arch in both feet. Thoracic kyphosis was increased, and the spinal axis in the thoracic region was deviated to the left with a fixed deformity. There was also excessive mobility of the elbow joints, thumbs, and little fingers of both hands, indicating moderate joint hypermobility.

An X-ray of the thoracic spine in two projections revealed a leftward deviation of the spinal axis, with the apex of the 7th thoracic vertebra, a curvature value of 50 according to the Cobb method, and increased thoracic kyphosis. The presence of joint hypermobility, flat feet, and kyphoscoliosis provided the basis for diagnosing the syndromic nature of the disease as JHS.

Clinical diagnosis was JHS, bilateral flat feet, left-sided kyphoscoliosis of the first degree. Given the syndromic nature of the disease, the child underwent a routine ultrasound and CT scan of the abdominal cavity. By chance, a large cyst of the lower pole of the spleen (67 x 52 x 47 mm) was detected (Figure 2B), and it was decided to perform a minimally invasive intervention using the Da Vinci surgical system through several minimal punctures in a specialised surgical institution.

For pathological examination, the macroscopic description revealed a unilocular cystic mass with a wall thickness of 0.2 cm, a smooth inner surface with slight trabecularity. The content was absent. The microscopic description, using Hematoxylin-eosin staining, showed that the cyst wall was composed of connective tissue, and the inner surface was lined with cuboidal and focally flattened epithelium. The pathological and histological conclusion (diagnosis) was an epithelial cyst of the spleen. The final clinical diagnosis included undifferentiated CTD syndrome, JHS, bilateral flat feet, left-sided kyphoscoliosis of the first degree, and a large epithelial cyst of the lower pole of the spleen. Postoperatively, the child's condition was satisfactory, with wounds healing by primary intention, and the sutures were removed seven days after the operation.

DISCUSSION

The study of CTD in children reveals a complex interplay of genetic, structural, and functional abnormalities affecting multiple organ systems. This discussion will delve into three pivotal areas: emerging diagnostic techniques, therapeutic advancements, and the psychosocial implications of CTD.

In our study, the process of diagnosing CTD was extremely complex. Advances in genetic research have significantly enhanced the diagnostic capabilities for CTD. Techniques such as WES and NGS have facilitated the identification of novel genetic variants, thereby improving our understanding of the molecular basis of these disorders. Additionally, 3D echocardiography and cardiac MRI have become crucial tools for early detection of aortic root dilation and valvular abnormalities, enabling timely interventions. Elastography, an imaging technique that measures tissue stiffness, is also being explored for its potential in the non-invasive assessment of connective tissue properties.[30]

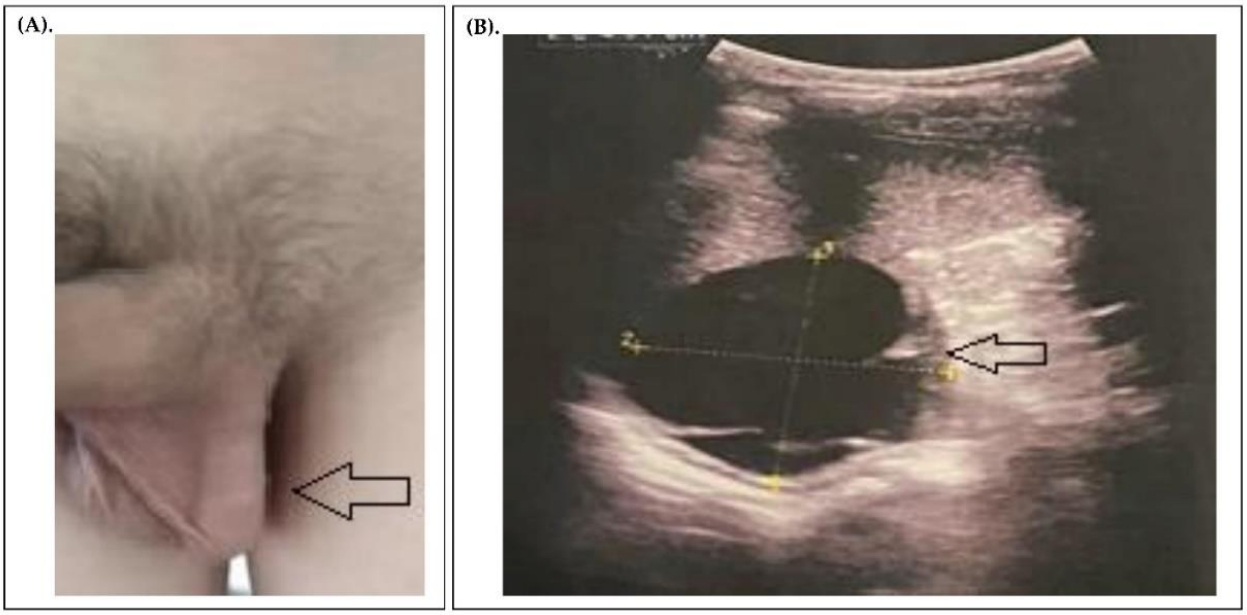

Figure 2. Clinical presentation and ultrasound findings. (A) Patient P, 15 years old, with varicocele of the left testicle. (B) Patient P, 15 years old, ultrasound showing a cyst of the lower pole of the spleen.

In our study, managing CTD presented its own set of challenges. Therapeutic strategies for CTD are evolving, with a focus on targeting the underlying molecular pathways. The use of angiotensin II receptor blockers, such as losartan, has shown promise in reducing aortic dilation in conditions like Marfan Syndrome by modulating the TGF-β signaling pathway. ERT and gene therapy are being investigated for specific subtypes of EDS, offering potential for disease-modifying treatments. Physical therapy, which emphasizes joint stabilization and muscle strength, remains a cornerstone of managing musculoskeletal complications. Additionally, innovative surgical techniques, such as minimally invasive endovascular interventions, are improving outcomes for vascular abnormalities like varicocele.[31]

The chronic nature of CTD, along with potential physical limitations and visible deformities, can profoundly impact the mental health and quality of life of affected individuals. Children with CTD often face significant psychosocial challenges, including anxiety, depression, and social isolation.[32] Multidisciplinary care teams, which include psychologists and social workers, are essential in providing holistic care that addresses both physical and emotional needs.[33-35] Support groups and community resources also play a critical role in helping families navigate the complexities of living with CTD.[35]

CONCLUSION

Dysplastic changes in connective tissue manifest as various clinical conditions, which should be considered in the comprehensive examination of affected children. The combination of undifferentiated CTD with

fibrous cortical defects, osteochondropathy, cystic changes in internal organs, and other developmental anomalies suggests that the study of this issue is still incomplete and requires further in-depth research.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
Patients have provided consent for the writing of this article.

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We have no conflict of interest

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