POSTGRADUATE MEDICINE
https://doi.org/10.1080/00325481.2022.2131439

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CLINICAL FEATURES
ORIGINAL RESEARCH

Congenital malformations of the urinary system as visceral markers of undifferentiated connective tissue dysplasia

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ABSTRACT

Objective: The relevance of this study is conditioned by the need for urgent search and implementation of effective methods of treatment of urinary system diseases in people of different ages, as well as addressing issues of quality treatment of connective tissue diseases in general and its dysplasia in particular. The aim of the article is to identify congenital defects as visceral markers of connective tissue dysplasia.

Methods: The methodology of this study includes a survey of a group of children with considerable problems in the development and functioning of the urinary system at the age of 2 weeks to 3 years, in order to qualitatively select and determine the most effective methods of treatment. Children who took part in this study had a set of phenotypic and clinical properties of undifferentiated connective tissue dysplasia.

Results: The considerable prevalence of undifferentiated connective tissue dysplasia in young children with congenital malformations of the urinary system, especially in children with abnormal development and functioning of kidney tissue, which substantially influences the course of the disease was determined. Also, treatment of undifferentiated connective tissue dysplasia was predicted.

Conclusions: It was concluded that the presence of a malformation of the urinary system, which is acquired by a child from birth, can be considered as a visceral manifestation of undifferentiated connective tissue dysplasia.

ARTICLE HISTORY
Received 7 December 2021
Accepted 29 September 2022

KEYWORDS
Connective tissue dysplasia; blood purification organs; childhood diseases; connective tissue

1. Introduction

The problem of renal pathology in children attracts the attention of pediatricians and pediatric urologists in connection with the growing number of nephropathies in children, increasing the incidence of congenital and hereditary forms, which in the early stages are complicated by inflammation of the kidneys and lead to a transition of the process into its chronic stage [1–4]. The growing number of congenital problems of formation, development, and further functioning of the urinary tract, which substantially adds relevance to the problem of identifying possible causes of their frequent development, as well as mostly initial diagnosis of congenital malformations of the urinary system organs (CM USO) and optimization of methods of treatment of uropathy in children of the first years of life, against the background of CM USO [5–8]. Over the last few years, there has been an increase in the incidence of microscopic abnormalities in various organs among children and morphogenetic cases of systemic changes due to the specific features of the structure and the existing state of connective tissue [9]. These changes are caused by a system of phenotypic traits and are defined as the undifferentiated connective tissue dysplasia (UCTD) [10]. Connective tissue dysplasia (CTD) constitutes an ontogenetic anomaly of the body's development, which should be attributed to complex, as yet undefined issues of modern medicine. CTD is described by various disorders of the visceral and locomotor systems with a progredient course, leading to a disorder of homeostasis at the tissue level, as well as at the level of organ functioning [10].

Connective tissue dysplasia is a genetically determined problem associated with disorders of connective tissue metabolism in the embryonic and postnatal stages and is described by abnormalities in the structure of extracellular matrix components with a progressive course of morpho-functional changes in individual systems and organs. Changes during the development of connective tissue dysplasia relate to various structural elements: biosynthesis and degradation of collagen, elastin, and proteoglycans [11]. Polyorganism and polysystemic lesions in connective tissue dysplasia are conditioned by the 'ubiquity' of this tissue and its important role in the functioning of organs and systems. To date, there are many studies on the

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pathology of the musculoskeletal system, bronchopulmonary, and cardiovascular systems in CTD. Connective tissue dysplasia can be caused by disruption of collagen synthesis at the stage of fibrillogenesis, as well as changes in its biodegradation, enzymopathy, disorders of fibronectin, elastin, glycoproteins, proteoglycans, including a small number of different cofactors of enzymes (magnesium, zinc, cuprum), ascorbic acid, oxygen, etc., which are involved in the formation of covalent bonds, playing a significant role in the stabilization of collagen structures, which are based on mutations in genes that cause the coding of the synthesis and spatial organization of connective tissue elements [12]. Congenital defects in collagen formation may underlie the creation of various congenital defects in the development of the urinary system, which creates the conditions for a considerable number of abnormalities in its development and diseases caused by chromosome and gene disorders resulting from external mutagenic processes in the fetal period [13]. Apart from a wide range of diseases, which are often based on gene defects, at present, there are mostly birth defects of connective tissue, which have a multifactorial nature [14].

Until recently, special attention was drawn to the study of undifferentiated types of connective tissue dysplasia, as these diseases are common, including in the practice of a pediatrician and pediatric urologist, and often underlie somatic pathology. There has been an increase in the number of children with somatic diseases associated with connective tissue dysplasia. It was proved that perinatal damage to the nervous system leads to a violation of the 'maturation' of morpho-functional structures of the urinary tract. Clinically, this manifests itself in the form of dysplasia of the pyeloureteral anastomosis, pathology of the vesicoureteral segment, etc. However, in the studies covering the undifferentiated connective tissue dysplasia (UCTD), little attention is paid to the risk factors for its occurrence in the antenatal and early postnatal periods. According to the authors, the study of cases of undifferentiated connective tissue dysplasia in children with congenital malformations of the urinary system is essential for their timely diagnosis and prevention of further occurrence. Planned detection of external phenotypic signs of the above connective tissue disease and their comparison with anatomical defects of renal development will allow to suspect connective tissue defects, to diagnose undifferentiated dysplasia of this tissue using biochemical and molecular genetic experiments and to obtain a correct understanding of the nature of the studied problems of development of the urinary system, and to make optimal therapeutic schemes taking into account the presence of pathological changes in the condition of connective tissue in the child. Early detection of undifferentiated connective tissue dysplasia in children with the above health problems will determine the choice of the most rational treatment, which would involve measures that can significantly improve the metabolic processes of connective tissue, which, in turn, would have a positive medical and social impact.

The purpose of the study is to establish the role of undifferentiated connective tissue dysplasia in the development of malformations of the urinary system, which are present in children from birth in the first years of life, suffering from secondary pyelonephritis.

2. Materials and methods

2.1. Study sample

Within the framework of this study, a medical examination was carried out for 210 children with congenital malformations of the urinary system and aged from 2 weeks to 3 years. Children who took part in this study had a set of phenotypic and clinical properties of undifferentiated connective tissue dysplasia. These children were examined in hospital and treated in the II Children's Department of the Lviv Oblast Children's Clinical Hospital (OCCH) 'Okhmatdyt' for 4 years.

The examined children were divided into four typical groups of research: Group I – children with abnormalities of development of kidneys of quantitative and positional nature – agenesis and doubling of kidneys, nephroptosis, and rotation of kidneys – 76 children (I – QPA), Group II – children with vesico-pelvic reflux of various degree – 67 children (II – VPR), Group III – children with hydronephrotic transformation of the kidneys – 53 children (III – HTK), and Group IV – children with abnormalities of development and differentiation of renal tissue – normonephronic hypoplasia and multicystic renal dysplasia – 14 children (IV – ADDRT). The control group included 65 children with pyelonephritis, nephro-urological examination revealed no CM USO – neither anatomical nor functional (V – Control).

2.2. Diagnosis and confirmation of the diagnosis

Confirmation of the diagnosis of pyelonephritis was performed based on clinical, laboratory, and instrumental examinations, in accordance with the 'Protocol for the diagnosis and treatment of pyelonephritis' (order of the Ministry of Health of Ukraine No. 627 dated 03.11.2008) [15], and the diagnosis of congenital malformations of the urinary system – according to standard, generally accepted in pediatric urology methods of examination of clinical, laboratory conditions and with the use of appropriate tools [16].

To verify the diagnosis of UCTD in children according to the method of qualitative reaction (according to the degree of turbidity), the level of oxyproline in urine was determined as an indicator of altered collagen metabolism and a common laboratory marker of connective tissue dysplasia. Urine to be examined was collected in the morning, a single portion, during clinical and laboratory remission of renal inflammation.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. A study was approved by National

Ethics Commission of the Ministry of Health of the Ukraine, 11 October 2019, No. 665-A.

2.3. Statistical analysis

Statistical processing of the results of this experiment was performed using Microsoft Excel and the application package Statistica 5.0 for Windows. To process the results that fall under the normal distribution, the authors of this study used a statistical method to determine the arithmetic mean (M), standard deviation (SD). Calculations of typical statistical values were carried out according to the general defined formulas.

Table 1. Distribution of examined children by groups and nosological types of congenital problems of development of the urinary system.

		Number of children	
	Nosological form	*n*	%
I – QPA	Complete unilateral or bilateral doubling of the kidneys	46	21.9
	Incomplete unilateral or bilateral doubling of the kidneys	21	10
	Pelvic dystopia of one kidney	4	1.9
	Agenesis of one kidney	3	1.4
	Kidney rotation	2	0.95
	Total	76	36.2
II – VPR	Unilateral or bilateral passive-active vesico-pelvic reflux II-III-IV centuries	67	31.9
III – HTK	Congenital hydronephrosis of I–II centuries	33	15.7
	Unilateral or bilateral congenital functional type pyeloectasis	20	9.5
	Total	53	57.1
IV – ADDRT	Normophronic hypoplasia of one kidney	6	2.9
	Multicystosis of the kidney	5	1.9
	Intraparenchymal cyst of the kidney	1	0.47
	Polycystic kidney disease, infantile type	3	1.4
	Total	14	6.7
	Total for all groups	210	100
V – Control	Acute pyelonephritis	55	84.6
	Chronic pyelonephritis, period of exacerbation	10	15.4
	Total	65	100

3. Results

The distribution of all children who took part in the survey, by nosological forms of malformations of the urinary system, received at birth, are presented in Table 1.

In children with pathology of the urinary system, a clinical and ultrasound examination was performed with an emphasis on the most frequently recurrent clinical-morphofunctional and visceral disorders, which are typical for undifferentiated connective tissue dysplasia. Manifestations of undifferentiated connective tissue dysplasia in children were diagnosed according to the criteria recommended by T.I. Kadurina [10], the results are presented in Table 2.

Most often phenotypic signs of UCTD were diagnosed in children of group IV with anomalies in the development and differentiation of renal tissue, in which almost all subjects had some signs of UCTD, namely: abnormalities in physical development in 78.6% of subjects, skeletal abnormalities – in 57.1%, in the skin and nervous system – in 35.7% of children, and in the gastrointestinal tract – in 21.4% of children. In children of groups I–III signs of undifferentiated connective tissue dysplasia were recorded with less and approximately the same frequency – in one-third of the examined, but significantly more often than in children of the control group without CM USO.

For the final confirmation of the diagnosis of UCTD in the laboratory, the level of excretion of oxyproline in the urine was determined. The results of excretion of oxyproline with daily urine in the examined children in comparison with the data of children in the control group are presented in Table 3.

Table 2. Phenotypic and clinical characteristics of UCTD in children with CM USO in their first few years of life.

	I–QPA, *n* = 76		II – VPR, *n* = 67		III–HTK, *n* = 53		IV-ADDRT, *n* = 14		V-Control, *n* = 65	
Body systems	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Lag in physical development, asthenic constitution	26	4.2*	4	20.89*	5	8.3*	1	8.6*	7	10.8
Gentle skin, thinning of the subcutaneous layer, increased skin elasticity	9	1.8*	8	11.9*	1	0.8*	5	5.7*	4	6.2
Soft nails	4	5.3*	3	4.5*	3	5.7*	2	14.3*	1	1.5
Thin, dull hair	2	2.6	1	1.5	2	3.8	1	7.1	–	–
Soft auricles	–	–	–	–	1	1.9	1	7.1	–	–
Diastasis of the abdominal wall muscles, muscle hypotension	12	15.8*	11	16.4*	11	20.8*	2	14.3*	5	7.6
Deformities of the chest and spine, various bone and cartilage dysplasia	7	9.2*	10	14.9*	11	20.8*	8	57.1*	3	4.6
Cardiovascular system: heart valve prolapses, false chords	2	2.6	2	2.9	4	7.5*	2	14.3*	1	1.5
Gastrointestinal tract: functional and anatomical defects of the gallbladder (membranes, inflections)	5	6.6	6	8.9	5	9.4*	3	21.4*	5	7.6

Note: * – statistically significant difference between the data of children with CM USO and the control group; $p < 0.01$

Table 3. The content of oxyproline in the urine of children with CM USO, $M \pm m$.

	Children groups									
	I – QPA, *n* = 76		II – VPR, *n* = 67		III–HTK, *n* = 53		IV-ADDRT, *n* = 14		V-Control, *n* = 65	
Indicator	$M \pm m$	%	$M \pm m$	%	$M \pm m$	%	$M \pm m$	%	$M \pm m$	%
Oxyproline in urine, conventional units	0.28 ± 0.03*	79.0*	0.13 ± 0.04*	57.0*	0.59 ± 0.08*	91.0*	0.71 ± 0.12*	100. 0*	0.06 ± 0.01	8.0

Note: * – statistically significant difference between the data of children with CM USO and the control group, $p < 0.01$.

The urine test for oxyproline was positive in the vast majority of all children examined. Oxyproline was excreted most frequently and in large quantities in the urine of children with abnormalities in the development and differentiation of kidney tissue – in 100.0% (0.71 ± 0.12 c.u., $p < 0.01$). In second place according to frequency and magnitude of oxyproline excretion were children with hydronephrotic transformation of the kidneys – 91.0% (0.59 ± 0.08 c.u., $p < 0.01$). Upon the laboratory study, urine oxyproline was detected in 79.0% of children with quantitative and positional abnormalities of the kidneys (0.28 ± 0.03 c.u., $p < 0.01$), the presence of free oxyproline in the urine was detected in more than half of children with vesicopelvic reflux (0.13 ± 0.04 c.u., $p < 0.01$), which significantly exceeded the indicators of children in the control group (0.06 ± 0.01 c.u., 8.0%), both in frequency and in arithmetic mean.

4. Discussion

Determination of the level of oxyproline in the urine of children with birth defects of the urinary system is evidence of the rapid breakdown and excretion of collagen metabolism products in the body of the child, in the vast majority of examined children of all groups. This is evidence of failure of connective tissue catabolism in the majority of children with CM USO and confirms the presence of UCTD in these children, and the malformation itself can be considered as a visceral manifestation of UCTD. The relatively low frequency of phenotypic manifestations of UCTD in these children is probably conditioned by the early age of the subjects, because according to the literature it is known that the incidence of phenotypic manifestations of UCTD increases with age [16,17].

Metabolic and energy imbalance, inherent in people with CTD, undoubtedly affects the nature of the course of various gastrointestinal diseases. According to the literature [18–20], 90% of people with connective tissue dysplasia are diagnosed with markers of catabolic processes in connective tissue and signs of mitochondrial insufficiency: decreased aerobic oxidative processes, activity of mitochondrial enzymes, and the predominance of anaerobic glycolysis. The presence of a wide range of energy cellular metabolism disorders in patients with CTD in the form of decreased peripheral blood lymphocyte succinate dehydrogenase activity, fasting hyperlactatemia, hyperuricemia indicates a violation of cellular energy metabolism, and undoubtedly affects the course of inflammatory and reparative processes. Thus, CTD is not only a special structural organization of organs and the body as a whole, but also an altered metabolic and biochemical constitution of a human being [11].

Connective tissue dysplasia as a certain level of holistic human organization, being an integral characteristic of individual-typological features of the dynamics of ontogenesis, metabolism, and reactivity of the organism, acts as the main characteristic of biological properties and reactivity of the organism in pathological processes, determines certain general patterns of pathogenesis and clinical course of associated gastroenterological diseases. Structural disorganization and functional inferiority of connective tissue in patients with CTD do not provide adequate anti-inflammatory and reparative properties of the mucous membrane in response to damage. Knowledge of dysplastic-dependent changes in the digestive system, pathogenetic and clinical features of gastrointestinal diseases in CTD avoids diagnostic and therapeutic errors in the supervision of this category of patients.

The strength of this study lies in the possibility of applying its results in practice to obtain opportunities to successfully treat kidney disease in children and prevent the spread of connective tissue dysplasia in young children. A potential limitation of this study is that the significant frequency of UCTD in the examined children requires a study of oxyproline content in their urine to determine the presence of connective tissue dysfunction, the confirmation of which would allow to reconsider opinions on the pathogenetic and therapeutic aspects of such patients. Verification of this condition among young children with CM USO, performed in the early stages, would help to qualitatively justify the metabolic correction of connective tissue dysfunction.

5. Conclusions

The results obtained in this study are convincing evidence of the high prevalence of undifferentiated connective tissue dysplasia among children in the first years of life with congenital malformations of the urinary system, especially in children with abnormal development and differentiation of renal tissue, because it would considerably affect the course of the disease and predicting its development and treatment options. In children suffering from malformations of the urinary system from birth, in all examined groups compared to the children of the control group, phenotypic and clinical signs of UCTD were recorded significantly more often. However, most often phenotypic signs of UCTD were diagnosed in children of group IV with anomalies in the development and differentiation of renal tissue, in which almost all subjects had some signs of UCTD. The obtained data indicate an important role of phenotypic phenomena of UCTD in children with CM USO.

Funding

No funding was received for the production of this article.

Disclosure of and financial/other conflicts of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

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References

1. Chu C, Li L, Li S, et al. Variants in genes related to development of the urinary system are associated with Mayer-Rokitansky-Küster-Hauser syndrome. Hum Genom. 2022;16(1):10.
2. Jain S, Chen F. Developmental pathology of congenital kidney and urinary tract anomalies. Clin Kidn J. 2019;12(3):382–399.
3. Dan H, Ruan T, Sampogna RV. Circadian clock regulation of developmental time in the kidney. Cell Rep. 2020;31(7):107661.
4. Makroum A, Abdelrazik M, Hassan M. Minilaparotomy for excision of a functioning noncommunicating rudimentary horn and endometrioma in a patient with solitary kidney: a case report. Gynaec Minim Invas Ther. 2020;9(2):91–94.
5. Huttanus HM, Vu T, Guruli G, et al. Raman chemometric urinalysis (Rametrix) as a screen for bladder cancer. PLoS ONE. 2020;15:e0237070.
6. Kuure S, Sariola H. Mouse models of congenital kidney anomalies. Advan Exper Med Biol. 2020;1236:109–136.
7. Shen Q. Progress in diagnosis and treatment of congenital anomalies of the kidney and urinary tract. Chinese J Appl Clin Paed. 2020;35(5):321–326.
8. Mazaheri M, Rambod M. Risk factors analysis for acute kidney injury in the new-born infants, predictive strategies. Iranian J Kidn Dis. 2019;13(5):310–315.
9. Nishimura B, Escalante J, Tuttobene MR, et al. Acinetobacter baumannii response to cefiderocol challenge in human urine. Scient Rep. 2022;12(1):8763.
10. Kadurina TI. Gorbunova VN Connective tissue dysplasia. St. Petersburg: Elbi; 2009.
11. Nechaeva HI, Lialiukova EA, Rozhkova M. Connective tissue dysplasia: main gastroenterological manifestations. Experl Clin Gastroenter. 2020;6:66–69.
12. Solienko OV, Rykalo NA, Osypenko IP, et al. Syndrome of undifferentiated connective tissue dysplasia: from the concept of pathogenesis to treatment strategy. Vinnytsia: Nova Knyha; 2014.
13. YeKh Z, Rak NO. Manifestations of undifferentiated connective tissue dysplasia from the cardiovascular system in patients with hypertension. AML XXI. 2015;2:14–18.
14. Tymochko-Voloshin R, Mukhin V. On the issue of connective tissue dysplasia in children: means of physical rehabilitation. Phys Activ Health Sports. 2014;1(15):46–53.
15. Order of the Ministry of Health of Ukraine No. 627. 2008. https://ips.ligazakon.net/document/view/MOZ8807
16. Paediatric urology: protocols of diagnosis and treatment of children in the specialty "Pediatric urology" (according to the Order of the Ministry of Health of Ukraine No. 624). https://ips.ligazakon.net/document/view/MOZ3136?ed=2010_05_12
17. Cui X, Liu T, Xu X, et al. Label-free detection of multiple genitourinary cancers from urine by surface-enhanced Raman spectroscopy. Spectroch Acta Part A Molec Biomolec Spectros. 2020;240:118543.
18. Hu D, Xu X, Zhao Z, et al. Detecting urine metabolites of bladder cancer by surface-enhanced Raman spectroscopy. Spectroch Acta Part A Molec Biomolec Spectros. 2021;247:119108.
19. Niankovskyi SL, Dobryk OO, Iskiv M. Metabolic therapy and its role in the complex treatment of connective tissue dysplasia in paediatric nephrology. Mod Paediat. 2016;1(73):131–136.
20. Verbitsky M, Westland R, Perez A, et al. The copy number variation landscape of congenital anomalies of the kidney and urinary tract. Nat Gen. 2019;51(1):117–127.