The Results of Laboratory Studies of Connective Tissue Dysplasia in Children Living in Yakutia

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ABSTRACT

Visceral disorders of various organs and systems in children with connective tissue dysplasia (CTD) living in extreme climatogeographic conditions according to laboratory tests have been studied. The children (35 schoolchildren) aged 10 to 17 years old were divided into mild, moderate and pronounced CTD degrees. Selection of children was performed by CTD phenotypic signs with score assessment and definition of CTD severity. The results of laboratory studies revealed more than 90% cardiovascular system disorders in children with CTD, about 85% of digestive system disorders and 70% of visual disorders, 50% of urinary disorders were detected in half of the children, mineral metabolism was impaired in 44% of the children. The connective tissue dysplasia in 70% of the children causes changes of 2 or more systems and organs, and in half (55%) causes 3 or more systems and organs disorders. When examining children with EchoCG, almost the majority of Cardiovascular Development Abnormalities (CDA) were detected. In more than half of children, 65.8%, i.e., 25 children were diagnosed with mitral valve prolapse (MVP). Mitral valve regurgitation was found in 28 children (73.8%), MVP of the 1st degree was noted in half of children with CTD, and the second degree was noted in 16% of the children and adolescents. In ten children (26%), abnormally located chords (ALC) were diagnosed, 13 children (34%) showed additional trabecules. The compaction of the calices-pelvis system walls occupies a special place in children with CTD.

Keywords: visceral disorders, connective tissue dysplasia, CTD, climatogeographic conditions, Yakutia

1. INTRODUCTION

The Republic of Sakha (Yakutia), located between 105°32′ – 162°55′ east longitude and 55°29′ – 76°46′ north latitude, covers the territory of 3103.2 thousand km2 and is completely located in the Far North and belongs to the regions of Russia, where the health of the population, including children, have extremely unfavorable indicators. The permafrost zone of cryolithozone, as the habitat of the population, is distinguished by its geographical, climatic and meteorological factors [1]. Complex effect of natural-climatic conditions and medical-social factors causes considerable tension of adaptive mechanisms of human organism, reduces its functional and immunological reactivity [2]. Extreme climatogeographic conditions in the Republic of Sakha (Yakutia) have a specific effect on the development of younger organism and its harmony. It is currently known that more than 50% of the population living in Russia has vitamin D deficiency. This condition is widespread in children, since in the North the daylight hours are very short and the duration of the cold season is 9 months per year, because of this, outdoor walks for children can be limited, and sometimes impossible [3].

Connective tissue dysfunction in the development of children, in most cases leads to the progression of the pathological state of various organs and systems. In recent years, the problem of connective tissue dysplasia has become increasingly urgent in connection with: the widespread practice of pediatricians and other specialists, the progressive course, the influence on the development of somatic pathology, leads to a decrease in the quality of life of children.

Any deviation from the norm can be accompanied by the progression of the pathological state of various organs and systems during the development of children.
Impairment of connective tissue in children is one of these abnormalities.

Cardiovascular Development Abnormalities are among the main visceral phenotypic manifestations of CTD. One of the most common and clinically significant valve apparatus abnormalities in children is mitral valve prolapse (MVP). In recent years, abnormally located chords (ALCs) in children have been considered as a manifestation of "CTD heart syndrome."

Impaired cardiac rhythm and conduction is one of the frequent pathological phenomena in dysplastic cardiopathy. [4]. The combination of CTD different symptoms deserves special attention. Spinal scoliosis, chest deformation, i.e. skeletal manifestations, affect the dense connective tissue. The gastrointestinal tract (GT) is necessarily involved in the pathological process in CTD. A high frequency of esophagitis, bowel diseases and gastroduodenitis in connective tissue dysplasia has been revealed. Neprhaptoses and kidney dystopathies most often exhibit changes from the urinary system in children with CTD [5]. Significant severity of bone mineral density reduction is observed in children with CTD.

Lack of comprehensive analysis of medical information (laboratory studies) left most children and adolescents with CTD without appropriate diagnosis and therefore do not receive the necessary recommendations for the lifestyle, treatment and work.

The purpose of the research. The purpose of our research was to study children with undifferentiated CTD by laboratory tests of various organs and systems living in the Republic of Sakha (Yakutia) in the form of Cardiovascular Development Abnormalities.

2. METHODS AND MATERIALS

The research included 35 schoolchildren of Yakutsk aged from 10 to 17 years old (average age – 13.75 ± 1.7) with a different CTD degree of severity, 17 of which were girls of average age of 14.2 ± 1.4 years, 18 young men whose average age was 13.1 ± 1.9 years. CTD verification was performed by scoring tables including phenotypic traits. A mild CTD degree was detected in 10 children (up to 12 points), in 18 – the average CTD degree (from 13 to 23 points) and in 7 adolescents – a pronounced degree (over 23 points). All children were identified during a pilot project studying the CTD prevalence among children and adolescents in Yakutsk. The study used vertebro-neurological examination methods, manual testing, measurement of muscle strength endurance. According to the medical record (form 026), the state of health of adolescents was assessed. All children had densitometry and plantography. Diagnosis of somatic diseases was carried out according to the MKB-10. Instrumental research methods included: ECG, EhCG with Doppler, ultrasound of abdominal organs and kidneys. Laboratory test methods included indicators such as calcium, iron, phosphorus, alkaline phosphatase and total serum bilirubin.

3. RESULTS AND DISCUSSION

Adolescents with mild CTD in the pathological process in most cases (80 %) involved one system (respiratory organs), in 20 % – two systems (GIS and CNS diseases). The average CTD degree was in 33.4 % of adolescents with 2 systems pathology, 66.6 % – 3 or more systems (more often CNS, OD, CVS). The pronounced CTD degree was in 85.7 % of children with chronic diseases, with 4 or more systems dysfunctions (CNS, OD, CVS, GIS, blood and hematopoietic system, etc.).

The half of the children with mild CTD during questionnaire had complaints of a single nature. The frequent complaint of 60 % children had recurrent and/or long catarrhal diseases (4 times and more in a year), is more rare – fatigue, leg, waist pains, waists, a sacrum generally connected with physical activity. Adolescents with a moderate and pronounced CTD degree made a lot of various complaints, mainly of asthenic-neurotic nature. Frequent complaints (about 70 % of adolescents) were rapid fatigue, headaches, irritability, frequent and protracted colds, dizziness, poor tolerability of exercise, heartbeat and pain in the heart area. A third of patients complained of joint pain (more often knee pain), abdominal pain, hiccup, burping, constipation, sleep disorders, weather sensitivity, dental bleeding, etc.

All adolescents had pathology of the musculoskeletal system. More often, schoolchildren revealed various posture disorders, flatulence, less often – chest deformities, scoliosis, visual impairment (myopia). The research used vertebro-neurological examination methods, manual testing, measurement of muscle strength endurance. Individual complexes of rehabilitation and recovery treatment were selected depending on prevailing pathology of CTD. The effectiveness of rehabilitation and recovery treatment was assessed by patient's well-being, subjective examination of emotional and psychological condition, dynamometry indicators and functional samples on muscle groups, spirometry, chest excursion towards the end of one course of treatment (14 days) and after 3 months.

Neurologist examination revealed residual encephalopathy in 2 teenagers of the 1st group. One case of residual encephalopathy with cervical-shoulder syndrome phenomena, hypotension in the hands, damage to the IX–X pair of cranio-cerebral nerves, and intracranial hypertension syndrome were diagnosed.
Another child has a diagnosis of residual encephalopathy with myotonic syndrome. In the 2nd group, 88.9 % of patients had neurological disorders: angioneurosis – 38.9 %, 2 children – residual encephalopathy, 1 – asthenoneurotic syndrome, intracranial hypertension, cerebro-asthenic syndrome, cervical spine instability, subduing S1 of cervical vertebrae. In the 3rd group – there were signs of angioneurosis in 3 children, in 2 – subversions S1 the cervical spine, with signs of vertebro-basillary insufficiency.

When studying obstetric history, we found that the majority (more than 70 %) of children with a mild CTD degree were born from physiologically occurring pregnancy. Half of the babies were from the first pregnancy and the first physiological birth. All children were born full-time. One child had a large birth weight. Hypoxia in childbirth with Apgar score of 6/7 points was recorded in the 1st child. Half (about 50 %) of children with a moderate degree, as well as 71.4 % – with a pronounced CTD degree, were born from pathologically occurring pregnancy. In half of the cases, children were from repeated childbirth, with short postpartum intervals. Pathology in childbirth occurred in 16.7 % of children with average degree and in 71.4 % with a pronounced degree of CTD. One child with a moderate CTD was born operationally. Two children with a pronounced CTD degree were born with a large body weight (one of them with a natal injury to the cervical spine and asphyxia) and one child in asphyxia (according to Apgar 6/6 points). Family history detected diabetes mellitus, bronchial asthma, diseases of the cardiovascular system, urinary organs and gastrointestinal tract in 30, 38.9 and 100 % of children with mild, moderate and pronounced CTD, respectively. For natural feeding up to 6 months, 60 % of children were with a mild CTD degree, 33.3 % were with average degree and 28.6 % were with a pronounced degree of CTD.

When performing somatometry, 40 % of children with a mild CTD degree, 38.9 % with average degree and 42.8 % with a pronounced CTD degree showed dysharmonic physical development, more often with a body weight deficit. 20 % of children with a mild degree, 50 % – with average degree and 71.4 % showed an asthenic type of constitution.

The neurologist diagnosed residual encephalopathy in 2 adolescents with a mild degree of CTD. In one case, RE with cervical-shoulder syndrome phenomena, hypotension in the hands, damage of the IX–X pair of craniocephal nerves, and intracranial hypertension syndrome. Another child has a diagnosis of RE with myotonic syndrome.

Children with average CTD degree revealed the neurologic disorders in 88.9 % of patients, 38.9 % of them had angioneurosis (A), 2 children had RE, one case – asthenoneurotic syndrome, neurogenetic dysfunction of a bladder, a syndrome of intracranial hypertension, a cerebro-asthenic syndrome, instability of cervical vertebrae, incomplete dislocation of C1 of cervical vertebrae.

3 children showed signs of angioneurosis, 2 – incomplete dislocation of C1 of cervical vertebrae with signs of vertebrobasilar insufficiency with a pronounced degree of CTD.

According to ECHO, almost all children with CTD were diagnosed with Cardiovascular Development Abnormalities. So, the majority of 53 % children, mitral valve tation regurga of the 1st degree was detected. Almost half of the children with CTD had regurgitation of the tricuspid valve in 48 % of adolescents. The open foramen ovale was diagnosed in 44 %, mitral valve prolapses in 41 % of children with CTD. It should be noted that half of adolescents foun an abnormally located chord in 47 %. 23 % experienced regurgitation of the pulmonary artery valves, then 16 % of children had diagonal left ventricular trabecula for the first time. Less than 10 % of the children were diganosed mitral valve regurgitation of the 2d degree (in 9 % of children), tricuspid valve prolapses in 6 %.

7 adolescents showed a conduction disorder, only two adolescents (5.3 %) had impaired repolarization processes according to the results of ECG. Heart rate disorder was found in 16 examined children, where tachycardia prevailed (14).

Hypermobility of joints (HMJ) is perhaps one of the most striking symptoms of systemic inferiority of connective tissue. HMI was found in more than 50 % of examined patients with CTD according to I.I. Ivano’s research. In the European population, the prevalence of CTD averages in about 10 %, in African and Asian slightly increasing from 15 to 25 %. There is a relation between HMI and the effects of sex hormones.

The change in the structure and relation of various types of collagens is associated with the development of HMJ. As a result of the weakness of the ligament apparatus, hyperlaxation develops in all or several joints, irregular posture, kyphosis, hyperlordosis, discopathy, scoliosis, flatulence and others are formed. In 20 children, that is, in almost half of the examined children, 52.6 % showed scoliosis. Most (52.6 %) of the children studied showed flatulence of the foot, mainly in young men. 4 girls (10.5 %) were diagnosed with osteopenia.

The leading place in the structure of digestive tract disorders belongs to the changes of the gallbladder. So, most 84 % (32 children) showed dyskinesia of the bile tract, 25 children had gall bladder deformation, 9 children had gall bladder wall compaction, which is 23.7 %, and three children had a S-shaped gallbladder. Parenchymal changes in the pancreas were diagnosed in
16 adolescents (42%). A compaction of the walls of the calices-pelvis system were diagnosed in 10 people (more than 26%) and three children was diagnosed with dysmetabolic nephropathy.

We can note the pathologies of the visual organs in children with CTD: 58% of myopia, myopia of the 1st degree in 42% of children, II and III degrees in only 6% of adolescents. Astigmatism was detected in 13% (5) of children.

Laboratory studies, such as a biochemical blood test, revealed a 44% decrease in serum calcium levels, and normal level of phosphorus in children. Blood iron results were lower in 6 children and higher in 4 children (10.5%). It should be noted that the indicators of total bilirubin in blood in 13% of children exceeded the norm. Such a serum indicator as alkaline phosphatase was found to be higher than the permissible norm in 10.5% (4) of adolescents. A complex clinical-laboratory examination of oral fluid in children with CTD living in Yakutia revealed a decrease in alkaline phosphatase activity regardless of severity, so the researchers note that children with severe CTD had a reduced concentration of total protein in saliva [6]. Ushnitsky I.D. et al., associate the features of the composition and properties of oral fluid with specific regional biological risk factors that can form the development of various pathological processes of oral organs and tissues in children with CTD living in the Far North [6].

Physiotherapy included: light therapy, magnetotherapy, halotherapy, and electrotherapy. There were contraindications for magnetic therapy and electrotherapy. Light treatment on the area of the pharyngeal lymphoid tissue ring received 40% patients from the 1st group, 27.7% – 2nd, 42.8% – 3rd group. Magnetotherapy (on the cervical, lumbar, intervertebral region) was carried out – in 60, in 22.2, and in 28.5% of patients, halotherapy – in 50, in 44.4 and in 28.5% of children, electrotherapy (more often with ephedrine according to Shcherbak) – in 20, 11.1, 28.5% of adolescents, respectively. Drug therapy included the prescription of energotrophic drugs (elkar, kudesan) – in 20, in 11.1, in 28.5% patients of the 1st, 2nd, 3rd group, respectively, macrolelements medications (magne B6, calcemin), vitamin therapy – to all adolescents, bacterial lysates (bronchomunal) – mainly to patients from the 1st group.

The treatment showed that 80% of patients from the 1st group significantly improved the condition, and 20% showed a moderate improvement. The 2nd group, 55.5% of adolescents had a significant improvement, a moderate effect – 33.3%, without changes – 2 children. The 3rd group found a significant improvement in 57.2%, a moderate effect – 28.5%, without changes – in 1 patient. All children stopped feeling fatigue, pain in the legs and back, sleeplessness, appetite. Children became emotionally calm, relations and contact with peers improved, became more sociable. There was an increase in physical qualities by 15% or more. Muscle strength and endurance increased; posture improved in most children of all groups.

After 3 months, most adolescents maintained their therapeutic effect. In patients who regularly continue medical exercises at home, physical indicators improved.

There is also no unequivocal opinion regarding the use of joint hypermobility as one of the leading diagnostic criteria for undifferentiated connective tissue dysplasia. It is believed that joint hypermobility can be a consequence of various metabolic and endocrine disorders (in particular, rickets) and a number of other reasons. In addition, this symptom is included in the symptom complex of differentiated connective tissue dysplasia syndromes (Marfan, Ehlers — Danlos syndromes, etc.). The difference between the hypermobile variant of Ehlers-Danlo syndrome and the so-called “benign articular syndrome” is unclear, and it is possible, according to T. Hermanns-Lê et al. (2012), the last presented is a mild variant of Ehlers-Danlos syndrome. It is extremely difficult to diagnose one or another hereditary syndrome in children without molecular genetic confirmation due to the significant overlap of signs in various syndromes, the vagueness of their manifestation and changes as the child grows.

Among the major diagnostic criteria for joint hypermobility syndrome is arthralgia lasting more than 3 months, not associated with inflammatory and traumatic injuries. At the same time, the majority of children with benign hypermobility of joints do not have any complaints. According to Yu.A. Lapkin (2009), arthralgias, synovitis, and back pain in children are associated not with joint hypermobility, but with other reasons.

Therefore, the author considers it inappropriate to use this feature for the diagnosis of undifferentiated connective tissue dysplasia [15]. In turn, the author associates foot deformities with dysplasia of the lumbosacral spinal cord, and considers scoliosis and chest deformities as independent diseases that can develop against the background of connective tissue dysplasia [15]. At the same time, L.N. Abbakumova (2009) showed that most children with arthritis have signs of connective tissue dysplasia, which are most pronounced in patients with chronic juvenile arthritis and in some forms of reactive arthritis.

As the author concludes, the erroneous inclusion of these arthritis in the chronic group leads to...
unreasonably aggressive treatment, which significantly worsens the prognosis of the disease. The results of the study by D. Czaprowski et al. (2011) indicate a high prevalence of joint hypermobility in children with idiopathic scoliosis and the need to take this into account when planning physiotherapy, since such children are vulnerable to soft tissue and joint injuries and they have an increased sensitivity of pain receptors.

4. CONCLUSIONS

Thus, a decrease in functional and immunological reactivity can be associated with a complex effect of natural and climatic living conditions (long cold winter, short summer, sharp temperature differences in seasons) and medical and social factors that cause significant tension in the adaptive organism mechanisms of children. Disorder of various organs and systems were found with the help of laboratory tests among children with CTD.

Cardiovascular disorders of more than 90% were diagnosed in children with CTD, then digestive disorders of about 85%, and 70% of visual disorders, urinary disorders were detected in half of the children (50%), mineral metabolism dysfunction was in 44% of the children. It was found out that connective tissue dysplasia in 70% of the children caused changes of 2 or more systems and organs, and in half (55%) caused 3 or more disorders. The majority of Cardiovascular Development Abnormalities were diagnosed in almost all patients by EchoCG. In more than half of children, 65.8%, i.e., 25 children were diagnosed with mitral valve prolapse. In 28 children, which is 73.8%, mitral valve regurgitation was found. Half of children with CTD revealed MVP of the 1st degree and the second degree (16%). In ten children, which is 26%, abnormally located chords (ALC) were diagnosed, 13 children (34%) showed additional trabeculae. The compaction of the calices-pelvis system walls occupied a special place in children with CTD, which, of course, requires further examination and treatment. According to the results of this research, therapeutic physical education or classes in special groups were recommended for all children with CTD, as well as rehabilitation treatment courses and specialists’ supervision. The balanced diet with additional vitamins, fatty acids, micro and macrocells in food was recommended to children with CTD.

The data presented reflect the uncertainty both in the diagnosis of undifferentiated connective tissue dysplasia and in the interpretation of its clinical manifestations. Isolation of individual nosological forms, in fact, representing manifestations of connective tissue inferiority on the part of any organ or system, disorientates the practitioner. There is a need for early detection of signs of connective tissue dysplasia, since some of them subsequently determine an unfavorable prognosis in terms of deterioration in the quality of life and the onset of disability.

And to exclude hereditary monogenic connective tissue disease in children with external phenotypic signs of dysplasia, further observation and careful examination are necessary.

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