SHERESHEVSKY–TURNER SYNDROME

Guidelines for the discipline "Medical Genetics"
for the training of interns, 5th year students
and cadet doctors of postgraduate education cycles

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
Харківський національний медичний університет

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СИНДРОМ ШЕРЕШЕВСЬКОГО-ТЕРНЕРА

Методичні вказівки
з дисципліни "Медична генетика"
для підготовки лікарів-інтернів,
студентів 5-го курсу та лікарів-курсантів
циклів післядипломної освіти

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I. Passport

1.1 Shereshevsky-Turner Syndrome (SST)

1.2 Code ICD-10:

Shereshevsky-Turner Syndrome (Q96)
Q96.0 Karyotype 45, X
Q96.1 Karyotype 46, X iso (Xq)
Q96.2 Karyotype 46, X with abnormal sex chromosome, except for iso (Xq)
Q96.3 Mosaicism 45, X / 46, XX or XY
Q96.4 Mosaicism 45, X / other cell line (s) with abnormal sex chromosome
Q96.8 Other variants of Shereshevsky-Turner syndrome
Q96.9 Shereshevsky-Turner syndrome, unspecified

1.3 For whom the protocol is intended (potential users)

Doctors-interns, 5th year students, doctor cadets of postgraduate education cycles, doctors and nurses of the KhISMGC-CR(O)D

1.4 Purpose of the protocol:

Identification and correction of metabolic disorders in SST.

1.4 Date of compilation: January 2017

1.5 Date of revision:

1.6 Order of the KhISMGC-CR(O)D on the development of local protocols

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1.7. The composition of the working group on the development of the local protocol "Porphyria"

Full name	Position
Grechanina Yelena Yakovlevna	General Director of the KhISMGC-CR(O)D, Corr. NAMSU, MD, professor
Grechanina Yulia Borisovna	Head of the Department of Medical Genetics, KNMU, MD, professor
Bugaeva Elena Valeriivna	Head of the Department of Clinical Genetics KhISMGC-CR(O)D, MD, associate professor
Tkacheva Tatyana Maksovna	Head of the cytogenetic laboratory KhISMGC-CR(O)D
Efremova Olesya Adamovna	Assistant, Department of Medical Genetics, KNMU

1.8 Medical and technological documentation at the industry level, on the basis of which a local protocol has been developed:

– Order of the Ministry of Health of Ukraine No. 751 dated September 28, 2012 "On the creation and implementation of medical and technological

documents for standardizing medical care in the system of the Ministry of Health of Ukraine";

– Order of the Ministry of Health of Ukraine No. 641/84 of 12/31/2003 "On the improvement of medical and genetic care in Ukraine";

List of abbreviations:

KhISMGC-CR(O)D	Kharkov Interregional Specialized Medical Genetic Center –- Center for Rare (Orphan) Diseases
LHCP	Local Health Care Protocol
RMGC	Regional Medical Genetics Center
IMGO	Interdistrict Medical Genetic Office / consultation
SST	Shereshevsky-Turner Syndrome
AP	Alkaline phosphatase
AST	aspartate aminotransferase
ALT	alanine aminotransferase
GGT	Gamma glutamyl transferase
MTHFR	Methylene tetrahydrofolate reductase
MTRR	Methionine Synthase reductase
MTR	Methionine Synthase
VDR	Vitamin D Receptors
PCR	Polymerase chain reaction
HDL	High Density Lipoproteins

1.8 Etiology.

Shereshevsky-Turner Syndrome (SST) is caused by full or partial X-monosomy, presented in all or part of the cells of the body. The relationship of the disease with a violation of the X chromosome was established by Ford in 1959. This chromosomal disease occurs with a frequency of 1 : 2 000 – 1 : 2 500 baby girls. Chromosomal abnormalities in this syndrome manifest as the absence of one of two chromosomes X: deletion of part of one chromosome X or translocation within the same chromosome X, various mosaic variants are also possible when the chromosome set is partially preserved. Only 1 % of embryos with karyotype 45, XO reach the fetal stage, others do not reach 28 weeks of gestation, about 10% of spontaneous abortions are associated with X monosomy. In some patients, the presence of chromosome Y (full or partial) in a number of cells is possible (option 45X/46XY clinically manifested by virilization, mixed dysgenesis of gonads is noted, is a risk factor in the development of gonadoblastoma). Typically, peripheral lymphocyte studies are performed to diagnose SST, but it is not able to detect deletions and translocations of chromosomes (D). The use of chromosomal sounding reveals such changes in the karyotype as a deletion or the presence of an isochromosome, and in the case of SST shows that complete monosomy 45X occurs only in 50–60 % of patients.

To date, it has been established that there is no clear correlation between the genotype and phenotype in SST (D).

1.9 Material and technical equipment:

Phonendoscope / stethophonendoscope, medical scales, height meter, centimeter in accordance with the equipment sheet.

Medicines – not used.

Disinfectants - Blanidas 300, Clinidez, Aerodezin, Lysoformin spec, Blanidas software, AHD.

II. The common part

2.1 Medical services provided

The center is a unique functional association of the Kharkov Interregional Specialized Medical Genetics Center - the Center for Rare (Orphan) Diseases, the Ukrainian Institute of Clinical Genetics, the Department of Medical Genetics of Kharkov National Medical University, and the association of specialists and families with a hereditary pathology:

• Ukrainian Association of Ultrasound Diagnostic Physicians in Perinatology, Genetics and Gynecology;

• Association of geneticists and families with children with phenylketonuria;

• Kharkov charity foundation "Cystic fibrosis" (an association of parents of disabled children with cystic fibrosis);

• The Future Generations Fund;

• Association of families with children with chromosome characteristics.

The main tasks of the KhISMGC-CR(O)D:

– organization of the provision of care specialized in the areas of genetics;

– carrying out three-level prophylaxis of congenital and hereditary pathology;

– the introduction of modern means of prevention, diagnosis and treatment of congenital and hereditary pathologies;

– analysis of the causes of perinatal and infant mortality from diseases in accordance with the direction of specialization and the development of preventive measures (genetic monitoring);

– statistical reporting on generalized regional indicators for established patterns, a systematic analysis of activities;

– ensuring continuity in work with health facilities on the prevention, diagnosis and treatment of congenital and hereditary pathologies;

– development of issues of social rehabilitation of patients;

– Providing feedback with LHCP and RMGC on issues of timely detection, quality of follow-up and treatment of patients with congenital and hereditary pathology;

– definition of a strategy and development of a set of measures for the functioning and further development of a certain area of medical genetics based on modern achievements of medical science and practice;

– providing advisory assistance, scientific, practical and organizational and methodological support to medical and genetic services institutions of various levels;

– development of basic regulatory documentation in a certain area: modern quality standards for conducting clinical and laboratory genetic examinations, criteria for assessing pathology;

– quality control of clinical and laboratory genetic examinations in areas of activity;

– Submission of proposals to health authorities to improve the relevant activities of the medical genetic services;

– advanced training of employees of healthcare institutions at various levels in the areas of specialization of the center.

When conducting genetic counseling, the geneticist abides the rules of bioethics and deontology. According to the current legislation, information on the hereditary nature of the disease in the proband or in the family is confidential and is provided to the person who was consulted. Medical specialists ensure the right of the patient about the need to inform other family members about the detected pathology.

In the case when a child or a person with reduced mental development acts as a proband, the results of genetic studies in the form of a conclusion are issued to parents or persons replacing them, in accordance with applicable law.

Operating procedure:

1. Patients with suspected metabolic disturbances are referred to the KhISMGC-CR(O)D for consultation.

2. The examination is carried out after collecting complaints, an anamnesis of the disease and life, building a family tree and conducting a clinical genealogical analysis, describing the phenotype by a geneticist and conducting a syndromological analysis, drawing up a genetic map.

3. The duration of the initial family consultation is 1.5 hours.

4. Regulatory documentation is drawn up in accordance with the requirements of the orders of the Ministry of Health of Ukraine.

Geneticist KhISMGC-CR(O)D:

Grechanina Ye. Ya. – General Director of the KhISMGC-CR(O)D, Corr. NAMSU, MD, professor, geneticist of the highest category

Grechanina Yu. B. – Head Department of Medical Genetics, KNMU, MD, associate professor, geneticist of the highest category

Molodan L. V. – Director of KhISMGC-CR(O)D, candidate of medical sciences, associate professor, geneticist of the highest category

Zdybskaya E. P. – Head of the metabolic center, candidate of medical sciences, associate professor, geneticist of the highest category

Bugaeva E. V. – Head of the connective tissue center, candidate of medical sciences, associate professor, geneticist of the highest category

Gulenko I. I. – Head of the Department of Genetic Monitoring, geneticist of the highest category

Biletskaya S. V. – deputy Director of the KhISMGC-CR(O)D for the medical part, geneticist of the second category

Krasov A. V. – Deputy Director for organizational and methodological work, geneticist

Adamyan L. M. – geneticist

Vernigora Oh. Yu. – geneticist

Grinyuk A. V. – geneticist of the first category

Grinchenko Yu. N. – geneticist

Evstigneeva O. V. – geneticist

Eliseev V. M. – geneticist

Elkova A. A. – geneticist

Zabelina A. A. – geneticist

Hmil O. B. – geneticist

Yanovskaya G. A. – geneticist of the first category

• has a valid local protocol

• obtains patient information consent for conducting genetic counseling and examination

• conducts qualified genetic counseling

• provides effective consultation on the results of the examination, provides information to the patient about his health status with recommendations for non-drug and drug treatment, behavior tactics in case of a sudden worsening of the course of the disease orally and in the form of an opinion

• maintains a list of patients with porphyria for dispensary observation; the list includes the following information: name, date of birth (in the format dd.mm.yy), address of registration and residence, contact phone number, diagnosis according to the latest wording, notes (additional information).

Nurse KhISMGC-CR(O)D:

• invites a family to an office for conducting genetic counseling

• treats the surface of the couch with a disinfectant

• prescribes referral for medical genetic counseling in accordance with the instructions of the geneticist

• fills in a statistical coupon for each patient

• calls for examination of patients from the dispensary group as directed by the doctor.

2.2 Diagnostics:

Geneticist:

– collects complaints, medical history;

– conducts a clinical genealogical analysis;

– assesses the phenotype;
– conducts syndromological analysis;
– directs to laboratory research, conducts an assessment (interpretation) of laboratory research;
– directs to instrumental methods of examination, evaluates (interprets) the data;
– conducts differential diagnostics;
– gives a diagnosis.

Nurse:
• writes out a referral for examination in accordance with the doctor's prescriptions;
• At 9.00 hours takes the test results daily
• informs the doctor about changes (if any) in the work of key points of medical care daily.

Place of research:

Type of study	Location	Note
Genetics appointment	Cab. No. 1, 5, 6, 7, 8, 10, 16, 19, 39, 46	
Blood sampling	Cab. No. 13	
Reception of morning and daily urine	Cab. No. 21	
Ultrasound examination of internal organs, thyroid gland, pelvic organs	Cab. No. 14	
Urinolysis	Cab. No. 21	
Daily urine test (calcium, phosphorus, hydroxyproline, GAG, urea, uric acid)	Cab. No. 21	
Blood biochemical profile (exercise therapy, total cholesterol, triglycerides, glucose, AST, ALT, urea, uric acid, creatinine, iron, CPA, LDH, GGT, total protein, albumin, total bilirubin, calcium, phosphorus)	Cab. No. 47	
High Performance Rare Chromatography of Blood Amino Acids	Cab. No. 47	
Blood lactate	Cab. No. 47	
Investigation of polymorphic variants of folate-methionine cycle enzyme genes (MTHFR C677T, MTRR A66G, MTR A2756G), VDR Bsml gene	Cab. No. 20	
Ultrasound procedure	Cab. No. 43,44,45	
Thyroid hormones (T4, TSH)	Cab. No. 31	
Homocysteine, blood vitamins (folic acid, B1, B2, B6, B12, 25-OH-D), trace elements (magnesium, zinc, selenium, copper), hormonal profile	Commercial laboratories	

2.3 Treatment

The goal of treating a patient with SST is to maximize the standard of living.

Geneticist:

- explains to the patient the features of the further development of the disease;
- gives recommendations for nutrition correction according to the results of the survey;
- prescribes drug therapy (cofactor therapy - vitamins, micro and macro elements, amino acids, antioxidants, energetic drugs, etc.) with proven effectiveness;
- draws up a plan of treatment and preventive measures for the patient;
- coordinate with the patient the scheme and regimen of medication;
- appoints planned visits of the patient to the doctor with an interval of 2 to 3 weeks to monitor the condition of the patient and conduct a follow-up examination (control of metabolic parameters that have been changed)
- issues an opinion with the results of the examination, a final diagnosis (if installed) and recommendations;
- planning consultations of related specialists (infectious disease specialist, immunologist, endocrinologist, allergist, gastroenterologist, etc.).

2.4 dispensary observation

Clinical observation is carried out for all patients with SST.

Geneticist:

– carries out regular medical supervision;

– appoints planned visits of the patient to the doctor to assess the tolerability, effectiveness and safety of treatment;

– monitoring the patient's implementation of the recommendations received is carried out with an interval of 2 to 4 weeks (until clinical improvement and normalization of the changed indicators are achieved);

– after achieving improvement in clinical manifestations and normalization of biochemical parameters, the interval between scheduled visits becomes more than 3 months

– monitors the implementation of recommendations, motivates and adjusts recommendations and appointments.

Nurse:

– in accordance with the prescriptions of the doctor invites patients to receive; invites three days before the recommended inspection;

– prescribes a referral for examination in accordance with the doctor's prescriptions.

III. Stages of diagnosis and management:

3.1 Algorithm for the diagnosis and management of patients with CBT

Chromosomal Suspicion	*Suspected Concurrent Metabolic Disorders*
Karyotyping	Urinolysis
FISH diagnostics	Daily urine test (calcium, phosphorus, hydroxyproline, GAG, urea, uric acid)
	Blood biochemical profile (LFK, total cholesterol, triglycerides, glucose, AST, ALT, urea, uric acid, creatinine, iron, CPK, LDH, GGT, total protein, albumin, total bilirubin, calcium, phosphorus)
Instrumental research methods	High Performance Rare Chromatography of Blood Amino Acids
	Blood lactate
	Study of polymorphic variants of folate-methionine cycle enzyme genes (MTHFR C677T, MTRR A66G, MTR A2756G)
	Thyroid hormones (T4, TSH)
	Homocysteine, blood vitamins (folic acid, B_1, B_2, B_6, B_{12}, 25-OH-D), trace elements (magnesium, zinc, selenium, copper),

3.2 Scheme of drug treatment of concomitant metabolic disorders

3.2.1 Violation of the folate-methionine cycle (patent for utility model "A Method for the Treatment of Autism" No. 91362, dated June 25, 2014, Ye.Ya. Grechanina, Yu.B. Grechanina, S. Beletskaya)

– diet therapy: with an increase in the level of homocysteine in the blood, exclude foods with a high methionine content from the diet;

– vitamin B6, betaine in age dosages;

– folic acid, vitamin B_{12} with a decrease in their level in the blood in combination with enrichment of the diet with products with a high content of them.

3.2.2 Mitochondrial dysfunction (see Local Protocol)

– restrict simple carbohydrates in food;

– the introduction of energetic drugs in an age-specific dosage: coenzyme Q10, L-carnitine, riboflavin, Medobiotin, succinic acid, dimephosphon.

3.2.3 Violation of the metabolism of vitamins

– dietary recommendations (enrichment of the diet with foods with a high content of deficient vitamin or restrictions on its excess in the body);

– with a deficiency of vitamin, its introduction in the form of a drug in an age-related dosage.

3.2.4 Violation of fat metabolism

– hyperlipidemia - lipid-lowering diet;

– hypercholesterolemia – fish oil in an age-related dosage; with hypertriglyceridemia – nicotinic acid in an age-related dosage;

– Decrease in HDL – resveratrol in an age-related dosage.

3.2.5 Impairment of purine metabolism

– restrict foods with a high content of purines (meat, fish and mushroom broths, meat of young animals, flour, smoked products, marinades, canned foods, tomatoes, eggplant, Puff pepper, sorrel, spinach, rhubarb, ketchup, mayonnaise, pastry cream, chocolate, sour fruits, high-fat dairy products, rosehip broth, black tea, coffee, carbonated drinks)

– allopurinol in an age-related dosage.

3.2.6 Impaired connective tissue metabolism (see Local Protocol)

– in the diet, restrictions on products made from premium flour, enrichment of the diet with products with a high content of vitamin C, collagen and products that stimulate its synthesis (homemade jelly, blue grapes, grape seed oil, 1 tsp broth from calf tails 3 once a day);

– Vitamin C at an age dosage.

3.2.7 Violation of the exchange of micro and / or macrocells

– dietary recommendations (enrichment of the diet with products with a high content of insufficient micro- and/or macronutrient or restrictions on its accumulation in the body);

– with a deficiency of micro- and/or macronutrient, its introduction in the form of a drug in an age-related dosage.

Treatment of each patient is carried out individually, taking into account a comprehensive assessment of metabolic disorders, the presence of intolerance to products and drugs.

3.3 Dispensary observation

Clinical observation is carried out for all patients with SST.

Навчальне видання

СИНДРОМ ШЕРЕШЕВСЬКОГО–ТЕРНЕРА

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