YAKUT MEDICAL JOURNAL 2(46)2014

# Clinical Description of a Rare Autosomal Recessive Syndrome in the Yakut Children

Gurinova E.E., Maksimova N.R., Sukhomyasova A.L.

ABSTRACT

The article describes the clinical signs (symptoms) of a rare storage disease in eleven Yakut infants. All the children were from unrelated families. The disease is very severe, leading to the disability and death at an early age. Diagnostics using the most complicated and advanced biochemical methods hasn't produced results.

**Keywords:** hereditary metabolic disease, lysosomal diseases, storage disease, Yakuts, Hurler-like phenotype.

INTRODUCTION

Inherited metabolic disorders (IMD) occupy a prominent place in the inherited human pathology. This place is defined as a large number of IMD, presently known, and a large number of patients with HMD, occurring in all populations are heavy and in most cases fatal manifestations [2].

Currently, more than 700 forms IMD. The vast majority of these diseases are caused by mutations in genes encoding enzymes, but also in this class include defects transport and signaling proteins. According to biochemical classification IMD divided into 22 groups according to the type of the damaged pathway (aminoacidopatologies, organic aciduria, etc.) or because of its localization in a particular compartment within the cell (lysosomal, mitochondrial and peroxisomal diseases) [3].

Clinical manifestations of the IMD is so diverse that there is no medical specialization, which would not have had to do with their specific spectrum of the IMD. The practical significance of the study is determined by purely medical aspects, the need to develop methods for diagnosis, treatment and prevention of these diseases that pose a serious challenge to modern health care. On the other hand, the IMD - the typical " biochemical " mutation of the human genome - is a powerful tool for the study of normal human metabolism, characterized by great complexity and a large number of "white spots " on your map [1]. Biochemical methods aimed at identifying the biochemical phenotype of the organism . The levels at which the measured phenotype can be different , from the primary gene product ( polypeptide chains) to the end of metabolites in the urine or sweat . Therefore, biochemical

methods are extremely diverse, and their importance in the diagnosis of hereditary diseases is increasing.

Due to the variety of biochemical methods used in the laboratory diagnosis of hereditary diseases, the use of these methods must be defined system. We surveyed the proband or a member of his family is unrealistic to eliminate all genetic disease that could be in sight in the survey . If we apply the possible number of methods of diagnosis, then every survey will be a very time- consuming and lengthy . That's why the original scheme of the survey is based on the clinical picture of the disease, genealogical data and biochemical strategies that allow us to determine the further course of the survey based on the phasing out of certain classes of diseases. In addition , a modern diagnosis of hereditary diseases is unthinkable without the genetic research [ 4].

Lysosomal storage diseases (LSD) now includes 45 different shapes. LSD are rare hereditary diseases. The frequency of individual forms is from 1 : 40,000 to 1 : 1,000,000 , and the total frequency of LSD estimated 1: 5000 - 1: 7000 newborns. Clinical manifestations are extremely diverse LSD from the earlier, manifesting fetal hydrops, to the lungs, benign forms that manifest themselves in the 5-6 months of age and did not significantly affect the quality and duration of life. In the presence of the expressed clinical polymorphism LSD characterized by steadily progressive course and lead to early disability and premature death [1].

MATERIALS AND METHODS

Data on the patients were obtained from the National Register of hereditary genetic and congenital disorders Medical -Genetic Counseling of Perinatal Center State Budget Institution Republic of Sakha (Yakutia) “Republican Hospital №1-National Medical Center”. Survey was conducted clinical geneticist 11 infants with the same clinical picture Hurler - like disease. Also, all children were examined by doctors of other specialties (cardiologist, pulmonologist, neurologist, orthopedicist, audiologist, ophthalmologist ).

RESULTS AND DISCUSSION

In the Medical -Genetic Counseling Department in Yakutsk from 2006 were counseling 11 children with Hurler-like phenotype: 7 girls and 4 boys. Eight children died before the 1,5 years old (including two boys) and one child died two years. All the children were from Yakut unrelated families. Parents are young.

Genealogical history of intermarriage was denied, but in most cases, both parents were natives of Vilyuiskaya region. Also a history of the two families, children from his first marriage were healthy. In one family, two children had Hurler-like phenotype, and died in infancy from

cardio-respiratory failure. In the same family of siblings sick children.

Medical history of that half of the children born from first pregnancy. During pregnancy birth defects, particularly heart defects, none of these children have not been identified (ultrasound investigation). There is information about visualization ventriculomegaly on II stage prenatal screening in one case.

All the children were born at term, full-term. Apgar score an average of 7-8 points.

Most of the children from birth or from a very early age (about 2 months) had so-called stigm disembriogenesis: heavy touch cheeks, nose, noisy breathing, on the hands all the fingers are slightly bent. Almost all children with the late neonatal period became concerned acute respiratory infections.

Onset of the disease was noted in an average of 4-5 months of age in the form of bronchial obstruction: noisy breathing, shortness of breath, coughing, high body temperature, heartbeat on the background of acute respiratory infection. Such acute conditions since the beginning tended to more frequent and each time the child's condition worsened, the increase of heart failure. Condition of patient became serious on valvular heart disease - first with mitral and tricuspid valves 1-2 degrees, moderate pulmonary hypertension. During 3-4 months disease is progressing, failure of the heart valves become 3-4 degrees and significant pulmonary hypertension.

All patients have similar clinical features:

- Dysplastic physique. In the dynamics of the delay in height and weight. With the progression of the disease forced position - sitting, lying. Long as the impossibility of lying on his back and on his abdomen.
- Face: gradual change like gargoilizm; hydrocephalic head closer to the hydrocephalic form, enlarged parietal tuber, low growth of hair on the forehead, hypertelorism, thick and thick eyebrows, long eyelashes, periorbital edema of the eyelids, wide noseband, a short nose with open nostrils forward, firm to the touch cheeks and nose, macroglossia.
- Skin: thick, relatively tight skin
- Skeletal: skeletal deformities, very short neck, chest wall deformity: barrel-shaped or bell-shaped, the shortening of the chest, stiff, wide aperture, mainly thoracolumbar kyphosis, lumbar spine, stiffness progression of small and large joints to contraction, claw –hand deformities, deepening palmar furrows.
- Respiratory system: the presence of bronchial obstruction, noisy breathing, shortness of breath increase, auscultation hard breathing, various dry and moist rales, the need for oxygen therapy.

- Cardiovascular system: tachycardia, hypertension, systolic murmur auscultation, birth heart defects, heart failure.

- Gastrointestina: enlarged abdomen due to hepatosplenomegaly, inguinal, umbilical, hernia non-operated (50%), without breaking the chair.

- Central nervous system: psychomotor retardation, development delay.

All children were conducted routin laboratory tests of blood and urine. Of the research results should be noted ultrasound investigation: hepatosplenomegaly, nephromegaly (3 cases). X-ray examinations showed signs of bone-destructive changes of the skeleton.

Echocardiography seven children after birth were identified congenital heart defects. One of them interventricular defect and atrial septal defect was detected on the 10 day, the remaining in the first six months of life. Five children was recommended surgery of CHD. Of these, four children were operated on, but one child died in the postoperative period, and the 5th child arrived. During echocardiography in all children were diagnosed with heart valve failure: the manifestation of the disease 1-2 degrees in the later stages - to 3 - 4 degrees, also showed signs of pulmonary hypertension at the beginning of a minor and in the end to marked degree.

As a result were excluded congenital hypothyroidism, cystic fibrosis, deficiency of alpha-1-antitrypsin, a chromosomal abnormality.

Medical history and clinical signs of possible suspect storage disease with Hurler-like phenotype. Due to the impossibility of challenging diagnosis in our respublic, analyzes and extracts children were sent to the federal Centers for enzyme diagnostic since 2006. In 2011, there were also investigated using dried blood spots on mucopolysaccharidoses types I and VI in the metabolic laboratory of the University Medical Center Hamburg (Germany). In 2013, one child was able to hold full-time counseling followed by laboratory diagnosis (enzymatic diagnosis, culture of skin fibroblasts to lysosomal storage diseases) in Department of Pediatrics Osaka University Graduate School of Medicine (Japan). Parallel biochemical study conducted in Lysosomal Storage Disease Section of Medical Department University of Cambridge (United Kingdom). Four out of eleven children were in a hospital examination of the federal medical centers (Moscow) like Institute of Pediatrics and Pediatric Surgery, Children's Clinical Hospital and National center of the healthy children.

During these years were excluded mucopolysaccharidoses I, II, III, IVB, VI, VII types , GM -1, 2- gangliosidosis , Gaucher's disease , mucolipidosis, disease Niemann -Pick type C / H / A, a hereditary amyloidosis, congenital disorder of glycosylation type I a, fucosidosis, mannosidosis, sialidosis, Krabbe, Fabry, Pompe. Despite the in-depth , sophisticated and modern

survey, accurate diagnosis for these children have not exhibited. But at the moment in Osaka University Graduate School of Medicine continues further research of this disease – the full genome sequencing for identification of the gene.

CONCLUSION

In conclusion, on the basis of clinical, genetic and instrumental and laboratory data described unverified rare recessive lysosomal disease with rapid progression and fatal in infancy. In this connection it's necessary to clarify the early diagnosis, which is made possible to due the full genome sequencing conducted in Japan.

BIBLIOGRAPHY:

1. Zakharova E.J. Enzyme replacement therapy in the treatment of lysosomal storage diseases / / Molecular genetic technology in medical practice. Issue 12. 2008, P. 231
2. Krasnopolskaya K.D. Hereditary metabolic diseases / / Handbook for physicians. Moscow, NGO "Center for social adaptation and rehabilitation of children" Fohat. "2005, P. 75
3. Mikhailova S.V., Zakharova E.J., Petruhin A.S. Neurometabolic diseases in children and adolescents. Diagnosis and treatment approaches / / Series "Practical Manual". Moscow. Publisher "Litterra." 2012, P.10, P.153
4. Therapeutic tactics correction of metabolic disorders in children with inherited metabolic diseases / / Ed. Novikov P.V. Moscow. Publisher "Overlay". 2011, P. 6-9.