CLINICAL CASE

S.N. Alekseeva, A.L. Sukhomyasova, G.I. Sofronova, Z.P. Androsova, S.A. Kondratieva, E.E. Gurinova, P.V. Pavlova

THE CLINICAL CASE OF PROPIONIC ACIDEMIA

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ABSTRACT

The article reports the clinical case of management of a child with a genetic metabolic disease until setting a correct diagnosis. Propionic acidemia is a rare genetic metabolic disease with autosomal- recessive type of inheritance which is related to metabolic desorder of organic acids. The early diagnostics is a difficult task because the clinical symptoms that are caused metabolic disorder, frequently occur by hypoxic - ischemic disorder of central nervous system, brain defects, fetal infections. The full - term child aged 11 days had developed metabolic crisis, which was taken as an expression of neonatal pathology, such as neonatal jaundice, perinatal CNS lesion. On a background of detoxification the patient has the clinical positive dynamic, every two weeks his condition improves. Due to a main disease the child had secondary immunodeficiency, which resulted in recurrent pneumonias. The patient N is examined in three ways: changes of peripheral blood - leukopenia, thrombocytopenia, anaemia; neurological symptoms - soporose condition, lethargy, refusal of meals, oppression of all reflexes, muscular hypotension; in view of anamnesis, impossibility of a comparison all the clinical symptoms to one diagnosis tap genetic research. The absence of the methodology of tandem mass-spectrometer in position extends the time of correct diagnosis establishing and timely treatment. In medical institutions it's necessary to identify levels of metabolites measured in various biological media (e.g. blood, plasma, cerebrospinal fluid and urine), glucose, lactate, pyruvic acid, ammonium, KET of b-hydroxybutyrate and uric acid.

Keywords: propionic acidemia, hereditary, metabolic diseases.

Introduction

Many congenital metabolic disorders in the neonatal period are very acute with the phenomena of metabolic decompensation, acidosis, vomiting, respiratory disorders. This symptomatology imitates the often acute infectious process. The nature of clinical changes is mixed. In addition to neurological disorders, a whole complex of severe changes in various organs and systems is found, i.e. the diseases are polished. According to the peculiarities of the course of the pathological process and the timing of the manifestation of the first clinical signs distinguish: Hereditary metabolic encephalopathies (NME) with manifestation in the period of newborn; NME with manifestation at 4-6 months of life; NME for 1 to 4 years of life; NME with manifestation in children of older ages [2].

Propionic acidemia (aciduria) -CODE ICD-10 E71.1 is a genetically heterogeneous hereditary disease from the group of organic acidemia caused by deficiency of propionyl-CoA carboxylase, which leads to blocking of propionate metabolism at the level of propionyl-CoA transfer into methylmalonyl-CoA and disruption of the metabolism of amino acids (isoleucine, valine, threonine, methionine), fatty acids with an odd number of carbon atoms and cholesterol. The disease occurs in different populations. The frequency among newborns in Europe and the USA is 1: 350,000. In some countries (for example, in Saudi Arabia) the frequency reaches 1: 2000. In the Russian Federation, the frequency of the disease is not defined. The disease is characterized by acute manifestation in the first days of life (with neonatal form), less often - in the first months of life (with infant form), occurs paroxysmally [3, 4].

Initial signs of the disease - vomiting, dehydration, refusal to eat, weight loss, infantile spasms, respiratory disorders (tachypnea, alternating apnea), generalized muscle hypotension, hyperreflexia, lethargy, drowsiness, coma. In some cases, draws attention to the peculiar face of patients: puffy cheeks, enlarged upper lip. Mortality at an early age reaches 40% [4].

Materials and methods of research

A pro-and retrospective analysis of the medical record of a stationary patient who was in the department of pathology of newborns and premature infants No. 1 of the Perinatal Center (PNND No. 1 PTC), in the oncohematological and psycho-neurological department No. 2 (PNO No. 2) of the pediatric center of the Republic of Sakha Yakutia "RB # 1-NCM".

Results and discussion

Child N. was born from his mother 26 years old, by the nationality Sakha, suffering from hearing loss of 3-4 degrees. From the anamnesis of life it is known that the woman has a complicated obstetric and gynecological history: the girl from the first pregnancy and the first marriage suffers from hearing loss, was born through natural birthmarks, during the second pregnancy Lues ill, the pregnancy from the second marriage at 26 weeks culminated in stillbirth. In occasion of Lues it was treated, from the account it is removed or taken off. The third pregnancy ended with a medical abortion at week 8. The fourth pregnancy, proceeded against the background of chorionamnionitis, operative clones in the gluteal the boy died on the 11th day of life in the central regional hospital with a clinical and pathoanatomical diagnosis: intrauterine pneumonia.

Child N. from the fifth pregnancy, which was without any peculiarities, the delivery operative on time, head presentation. The indication for surgical delivery was a complicated obstetrical anamnesis, a scar on the uterus. Clinico-histologically confirmed chorionamnionitis. According to the physical parameters, the child corresponded to gestational age, birth weight 3460, height 52. The Apgar score was 8/8. The early neonatal period was uneventful. After receiving the vaccination against hepatitis B and BCG, after audioclearning in the obstetric hospital and neonatal screening for 5 hereditary diseases were prescribed home on day 6 from the obstetric hospital.

On the 11th day of life, he enters the PNND No. 1 PTC with complaints of jaundice and lethargy, refusal to eat. At objective examination, the saffron color of the skin is noted, the weight at admission is 3140 (-320 grams, 9.2%), the cry is weak, the symptoms of CNS depression are noted: general muscle hypotension and hyporeflexia, the child refuses to feed. At admission, the diagnosis is: Bilirubin encephalopathy? In the clinical picture intercurrent infection - acute pneumonia of unclear etiology, neonatal sepsis joins. In a laboratory study, the level of total bilirubin is 280 μmol / l. A general analysis of blood determines leukopenia, and periodic thrombocytopenia (see Table 1). In the immunogram, cellular immunodeficiency is detected (see Table 2). On the RCT of the lungs at the age of 14 days: bilateral polysegmental pneumonia, subsegmental atelectasis of the

left lung was detected. Against the background of ongoing therapy: phototherapy, detoxification therapy, antibiotic therapy, immunoglobulin replacement therapy, immunomodulatory therapy, the child gives positive dynamics. He becomes quite active, eats milk formula, the mother refuses breastfeeding. When assessing the neurological status, the lack of communication is alarming, when audioclearing it is revealed that the child is at risk for hearing loss. According to the MRI of the brain at the age of 25 days, a small delay in myelination in the substance of the cerebral hemispheres is determined. Easy ventriculodilation of the lateral ventricles without signs of excessive intraventricular pressure. Patient N. is diagnosed with:

Primary: Bronchopneumonia, unspecified. Bacterial sepsis of the newborn.

Concomitant: Perinatal CNS damage of mixed genesis, severe. There's a risk of hearing loss. Neonatal jaundice.

At the age of 1,5 months he is discharged home, with the appointment of a neurologist, a course of pantogam.

In two weeks he enters the Pediatric Center with the diagnosis: Anemia of early age. Neutropenia. Dose-dependent side effect of pantogam? Complaints about drowsiness, oppression, prolonged sleep, refusal to eat. From the anamnesis of the disease it is known that it became sluggish and drowsy on the 15th day after being discharged from the PNSN # 1 of the PTC RS(Y) «RB # 1-NCM». Patient N. is examined in three directions: changes in peripheral blood - leukopenia, thrombocytopenia, anemia; neurologic symptoms - co-morbidity, lethargy, refusal to eat, oppression of all reflexes, muscle hypotension; taking into account the anamnesis, the impossibility of comparing all the clinical symptoms under one diagnosis is connected with genetic research.

Peripheral blood indices determine persistent leukopenia up to 0.8x10 9 / l, a periodic decrease in hemoglobin and platelet levels (see Table 3). The acid-base state of the blood is determined by persistent metabolic acidosis: pH = 7.22, BE = 12 mmol / L. In the myelogram at the age of 2 months 4 days, there was an increase in the proliferation of elements of the megakaryocytic germ with signs of dyspoezia, as well as mild eosinophilia - 7.75%, at the age of 2 months 10 days, severe inhibition of the granulo-megakaryocytopoiesis elements profiling is a manifestation of the hypoplastic process.

The peculiar face of the patient was paying attention: puffy cheeks, enlarged upper lip. During the period of the metabolic crisis, there is a sign of soporus, refusal to eat, vomiting, convulsions. Against the background of ongoing detoxification therapy, there is a short-term improvement in well-being. The patient begins to show hunger, the sucking reflex is activated, gaining weight. During periods of stabilization of the state, improvement in the dynamics of blood indices is determined, regression of convulsions.

According to the MRI of the brain at the age of 2 months, 4 days, symmetrical areas of ischemia are defined in the cortical areas of the parietal lobes, in the thalamuses and in the central parts of the cerebellar hemispheres on both sides. MR-signs of perinatal encephalopathy. To all symptomatology the infectious process joins, nosocomial segmental pneumonia: at the age of 2 months 9 days - CT signs of interstitial infiltration in S6, 9 of the right lung, S 6, 10 of the left lung. According to electroencephalography, the picture of the coma is determined. Primary-genitalized epileptic activity, not associated with tremor attacks. Clearly focal activity was not revealed. EEG at the age of 2 months 9 days: EEG picture of the pattern «flash-suppression». During the treatment period the child was examined by a neurologist, an ophthalmologist, a geneticist, a surdologist, hematologist. At a biochemical blood test: glucose 5.68-5.8 mmol / l, the state of hypoglycemia was not determined by analysis, urea 3.7 moles / l, creatinine 39.1 mkmol / l, lactate 5.24 mmol / l, with load 7.65 mmol / l.

Analysis of clinical and laboratory data made it possible to suspect a hereditary metabolic disease. On the issue

Table 1

Indicators of a CBC in the admission dynamic in Neonatal Pathologies and Special Care Nursery

Days of life	Leukocyte 10 9/l	RBC 10 12/l	Нв, g/l	Ht, %	Thrombocyte 10 9/l
11	4,5	4,97	170	51,2	192
12	4,5	4,53	152	46,7	144
13	2,5	4,07	137	41,8	47
15	3	4,2	152	48,5	58
21	6,2	3,2	113	32,1	390
24	8,2	3,29	110	34	494
30	7,9	3,38	109	34,1	324
35	7,2	3,2	111	32,7	474
44	5,8	3,02	105	30,1	191

Table 2

The dynamic of the patient's N immunogram

Age	IgA	IgM	IgG	ЦИК	CD 3+	CD 4+	CD 8+	CD4/ CD8	CD 19+	CD 20+	CD 25+	CD16+ CD 56+
16 days	1,65	0,96	10,5	99,7	87	70	17	2,6	4	3	14	7
1 months 5 days	0,6	0,96	5,27	93,5		52	20	2,6	12	9	9	12
2 months 5 days	1,45	4,11	7,46	91,98	79	55	27	2,04	2	1	5	18
2 months 13 days	1,82	0,82	6,64	93	87	70	17	2,6	4	3	14	7

Table 3

Indicators of a CBC of the patient N in the dynamic at the first time of hospitalization in the Pediatric Center

Age	Leukocyte 10 9/l	RBC 10 12/l	Нв, g/l	Ht, %	Thrombocyte 10 9/l
2 months 2 days	1,9	2,85	93	26,1	303
2 months 4 days	1,5	2,55	81	23,1	179
2 months 5 days	1,7	4,14	107	32,2	102
2 months 10 days	1,8	4,22	114	32,4	28
2 months 19 days	3,0	3,58	98	28,7	400
3 months	3,3	3,29	95	25,8	713
3 months 3 days	2,4	3,27	95	27,2	580
3 months 6 days	0,8	2,99	91	25,1	133
3 months 7 days	1,3	3,29	98	27,6	44

of diagnostics and risk of physicians, remote consultation was conducted with the federal scientific and clinical center of pediatric hematology, oncology and immunology named after Dmitry Rogachev, FGBU «Russian Children's Clinical Hospital» of the Ministry of Health of the Russian Federation, FGBU «Medical Genetics Research Center» RAMS. Blood samples were sent to the laboratory of hereditary diseases of the FGBU «Medico-Genetic Scientific Center» RAMN for tandem mass spectrometry. Based on the results of the study, an increase in the concentration of propionylarnitine was detected, the methylmalonic acid test was negative. The significant increase in organic acids in the blood in combination with the characteristic clinical manifestations made it possible to diagnose the propionic acidemia, the neonatal form in the child.

After confirmation of the diagnosis, the treatment strategy was based on the following principles: limiting the intake of isoleucine, valine, threonine and methionine with food to the minimum requirement; administration of levocarnitine to enhance the binding of the toxic propionyl radical; Exclusion of starvation, prevention of activation of catabolism; controlling the acid-base state of the blood, preventing the development of acidosis, maintaining the water balance; increased therapy during the metabolic crisis [1, 3].

Despite intensive therapy, the child's specific nutrition died from multiple organ failure and toxic encephalopathy due to severe metabolic acidosis. The patient N. lived 3 months 11 days. The pathoanatomical diagnosis is exposed: The basic disease: Hereditary illness of an exchange. Propionic acidemia. (E 71.1).

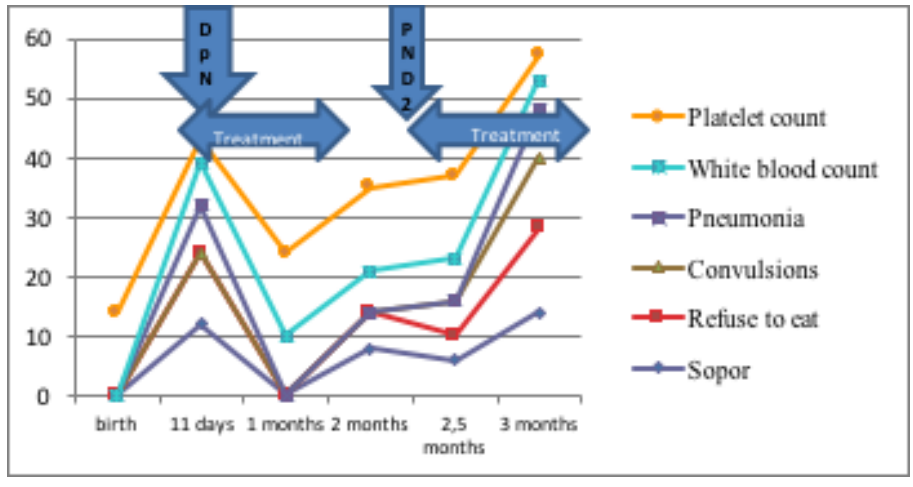
Complications of the underlying disease: Aplastic state of blood: agranulocytosis, anemia, neutropenia, thrombocytopenia (D 60-70). Secondary necrosis of the gastric mucosa, small intestine. Gastrointestinal bleeding. DIC-syndrome: hemorrhage under the epicardium, mucous membranes of the respiratory tract, esophagus, serous membrane of the large intestine. Subarachnoid perivascular hemorrhages.

Focal hydropic and fatty liver. Ascites. Hydropericardium. Cerebral edema.

Concomitant diseases: Simple kidney dysplasia. Hearing loss according to clinical data. Comparison: coincidence. Cause of death: Progression of the underlying disease. Category of difficulty: II.

Conclusion

This clinical example shows a long diagnostic search, late diagnosis and attracts the attention of neonatologists, resuscitators, pediatricians, neurologists to the diagnosis of hereditary metabolic diseases. The absence of a screening diagnostic technique postpones the precious time of setting the right diagnosis and prescribing specific therapy.



The dynamic of clinical displays of patient N at the second time of hospitalization

A thorough clinical examination of the child and the definition of the symptom complex contribute significantly to the success of the differential diagnostic process, which consists of 4 stages. Each of the stages has its own tasks:

Stage 1 - provides for the examination of children with undifferentiated pathology and the delineation of hereditary and non-hereditary diseases. In this case, special importance is attached to the clinical symptom complex, given genealogy, obstetric anamnesis.

Stage 2 - is characterized by the identification of children with a possible hereditary pathology of amino acid metabolism and the determination of their dominant clinical symptoms. The doctor is recommended to compare by the presence of dominant signs with six groups of hereditary aminoacidopathies: 1 - diseases accompanied by ketoacidosis and vomiting, 2 - diseases accompanied by a change in color and odor of urine, 3 - diseases accompanied by eye pathology and mental retardation, 4 - diseases accompanied by CNS and liver damage, 5 - diseases accompanied by mental retardation and convulsive syndrome, 6 - diseases accompanied by psychoneurological disorders and skin lesions.

Stage 3 - intra-group differential diagnosis is performed.

Stage 4 - a purposeful laboratory examination. Efficacy is determined by the thoroughness of the examination in the first three steps [2].

Thus, at the pre-laboratory level of the survey, the use of purely clinical signs allows to significantly reduce the number of nosological forms for differential diagnosis and determine the nature of subsequent laboratory studies.

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Information about authors:

Yakutsk, Republic Sakha (Yakutia), Russia:
1. Alekseeva Sargylana Nikolaevna – PhD, Associate Professor of the Department of Pediatrics and Pediatric Surgery of the MI SVFU, sargylanao@mail.ru;
2. Aitalina Lukichna Sukhomyasova, PhD, Head of educational and scientific laboratory "Genomic medicine" NEFU, head of medical-genetic center of GAU RS (Y) "RB # 1-NCM", AitalinaS@yandex.ru;
3. Afanaseva Natalya Aleksandrovna – neonatologist of CDN of Nam district.
4. Sofronova Gulnara Ivanovna - PhD, a neurologist of the highest qualification

category of psycho-neurological department №2 of GAU RS (Y) "RB # 1-NCM", gulnara-ykt@yandex.ru;
5. Androsova Zinaida Petrovna - PhD, a neurologist of the highest qualification category of the psycho-neurological department No. 2 of GAU RS (Y) "RB # 1-NCM";
6. Kondrateva Sargylana Afanasyevna – head of oncohematology department, a pediatric oncologist and hematologist of the highest qualification category, gematologia@mail.ru.
7. Gurinova Elizaveta Egorovna - doctor-geneticist of the medical-genetic center of GAU RS (Y) "RB # 1-NCM".
8. Pavlova Paraskovya Vitalievna - 6th year student of the Pediatric Department of the Medical Institute of NEFU named by M.K. Ammosov, paraskpopova@mail.ru.

EXPERIENCE EXCHANGE

A.A.Yarovskiy

MEDICAL AND STATISTICAL ASPECTS OF STUDYING THE INCIDENCE OF ABORTION IN THE SAKHA REPUBLIC (YAKUTIA)

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ABSTRACT

The article represents the results of medical and statistical analysis of abortion in the Sakha Republic (Yakutia) for the long-term period (1991–2015). A decrease in the incidence of abortion and transformation of its structure has been noted. The level of abortions due to social indications and registered criminal abortions has decreased the most. An increase in the proportion of spontaneous and unspecified abortions in total ratio of abortion has been found out. The results of the correlation analysis confirm the influence of the women reproductive behavior on demographic processes in the Sakha Republic (Yakutia).

Keywords: abortions, reproductive losses, demographic processes.

Introduction

One of the most important tasks of the Russian Federation State Program "Health Development" is the ensuring of the prevention in the sphere of health care and the development of primary health care for the population. In the subprogram "Mother and Child Welfare" particular attention is paid to prevent and decrease the number of abortions. Priority of ongoing measures is determined by social and demographic processes characterized by stable depopulation, population aging and health deterioration of all population groups [3, 4, 6].

Under modern demographic conditions the problem of demographic losses is very actual because despite its constant downward trend, abortion takes a leading place in realization of women reproductive function and structure of reproductive losses [1, 2, 5]

The aim of the research is medical and statistical analysis of all types of abortions structure and incidence dynamics followed by evaluation of their influence on demographic processes in the Sakha Republic (Yakutia).

Materials and methods

To achieve the aim of the survey retrospective analysis of abortions structure and dynamics of their incidence in the Sakha Republic (Yakutia) for the long-term period (1991-2015) was carried out. Base material was a Form of state federal statistical observation №13 "Information on termination of pregnancy (up to 22 weeks)" (n=25). The indicators of abortions frequency calculated for 1,000 women of fertile age and 100 normal births were analyzed. The indicators of abortions frequency and their dynamics in different reproductive age groups for the given period were analyzed. The dynamics of the abortions level in early and late terms of pregnancy termination was compared. The dynamics of abortions among primigravidae was determined.

To analyze the correlation between reproductive-demographic indicators and abortions Pearson correlation analysis was carried out. The base of the analysis was statistical data of the Territorial body of Federal State Statistics Service in the Sakha Republic (Yakutia) for the period 1990-2015. The strength and direction of the relationship between the variables were estimated. The distribution of quantitative variables was under the normal law (p for the Shapiro-Wilk criterion more than 0.05).

Results and Discussion

The study of reproductive function realization in the Sakha Republic (Yakutia) at 2015 year-end shows 16,379 (59.3%) pregnancies end with childbirth; 11,236 (40.7%) end with abortions. In 2015 the number of abortions for 1,000 women of fertile age was 46.2 (in the Russian Federation – 23.8).

The data on spontaneous, induced and unspecified abortions were analyzed to understand better the nature of pregnancy terminations. As a result, changes in the structure of abortions types were determined (Figure 1).

The percentage of spontaneous abortions increased by 14% over the period under review, the share of unspecified abortions increased by 5.7%, the share of induced abortions decreased by 19.2%. In 2015, 21.0% of the abortion structure were spontaneous, 7.9%, unspecified abortions, 4% - justifiable abortions, and 67.1% legal medical abortions.

The total number of abortions for the period 1991-2015 decreased from 30,062 to 11,236 mainly due to legal medical abortions, number of which decreased by 64.7%.

Analyzing the incidence of abortions according to their types the uneven dynamics of indicators rates attracted attention. The rate of abortions having the greatest medical and social significance - abortions for social indications and registered criminal ones - decreased to the maximum extent.

The incidence rate of justifiable abortions remained stable at 1.8 per 1,000 women of fertile age for the period under review. The number of unspecified abortions increased by 35.8% (Figure 2).

For the period 1991-2015 the prevalence rate of spontaneous abortion as the main indicator of women reproductive health increased from 7.5 to 10.1 per 1,000 women of fertile age (Table 1). The share of spontaneous abortion in 2015 was about 11% of the number of pregnancies ended with childbirth.

Since 2012 in the structure of abortion