Hereditary Disease Epidemiology Study as the Basis for Pharmacotherapy Need Determination among Newborns

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Abstract

According to the screening data of newborns in the Belgorod region (2006 - 2013) the article determined the frequencies of hereditary metabolic diseases in order to establish the need for pharmacotherapy. The frequency of phenylketonuria (PKU) among newborns made 1:7831, cystic fibrosis (MV) - 1: 12103, congenital hypothyroidism (CH) - 1:4930, adrenogenital syndrome (AGS) - 1:13313, galactosemia (GAL) - 1:33284. There are 58 children with hereditary metabolic diseases and the need of pharmacotherapy in the Belgorod region (2006 - 2013).

Keywords: Hereditary Diseases, Metabolism, Screening, Phenylketonuria, Cystic Fibrosis, Congenital Hypothyroidism.

Introduction

Currently, there are numerous modern data on the prevalence, clinic, diagnosis, including prenatal and neonatal, of frequently occurring hereditary diseases (HD), the study period for prenatal diagnosis and the obtained data interpretation. Despite the results of complex medical and population genetic studies of hereditary diseases among children [10, 11], the problem of early diagnosis, pharmacotherapy and HD prevention has not been resolved fully. It should be noted that the population-genetic aspects of these diseases have been studied only in certain regions of Russian Federation, although the development of HD genetic epidemiology issue is of fundamental importance both from practical and theoretical point of view.

Modern pharmacogenetics seeks to identify genes and their variants that determine the adequacy of pharmacotherapy and reduce the risk of side effects [6, 27, 28]. Nowadays they determined the associations of polymorphisms of several candidate genes with the development of the most common multifactrial diseases [9, 13, 14, 15, 22, 23] and showed the genetic determination of congenital and chromosomal diseases [8, 21, 24]. Significant advances in the development of molecular genetic testing methods and technologies allow in most cases to carry out molecular genetic diagnostics of some HD successfully. The greatest difficulty is the evaluation of the contribution to the development of rare and previously unidentified disease mutations, as well as the determination of genotype-phenotype relationship and the influence of modifier genes on the disease severity.

Recently, the interest in hereditary metabolic diseases (HMD) has been increased. Hereditary metabolic diseases include more than 700 nosological forms. These diseases are associated with the disorders of a particular metabolic pathway. These include: phenylketonuria (PKU), congenital hypothyroidism (CH), galactosemia (GAL), adrenogenital syndrome (AGS) and cystic fibrosis (CF). These diseases are related to such pathologies in which timely initiated treatment can prevent the development of serious diseases and severe disabilities, as well as reduce the economic costs associated with pharmacotherapy, social rehabilitation and life support for disabled people. For several decades, mass screening and selective screening programs have been used for the purpose of HMD early detection. However, it should be noted that the population-genetic aspects of these diseases were studied only in certain regions of Russian Federation [1-4, 7, 12, 18, 19, 25, 26].

The results of phenylketonuria monitoring among children and adolescents in the Sverdlovsk Region showed that a pronounced economic effect is achieved with the implementation of the mass screening program, i.e. the total cost of screening tests and treatment is several times less than the cost of maintaining undiagnosed patients who are disabled. According to foreign authors, the ratio of the economic benefit from the saved work capacity to the funds spent on the screening program and the treatment of patients is from 1.8 to 7.9 for PKU (Work summary ..., 2005). The economic efficiency of neonatal screening for Russia, calculated according to the State Statistics Committee data, makes 3.74, taking into account 90% of identified sick children.

With the increase of identified patient percentage to 100%, the efficiency increases up to 4.33 [20].

In accordance with the mentioned above, this article analyzes the epidemiology of hereditary metabolic diseases to determine the need for pharmacotherapy among the newborns in the Belgorod region.

Materials and Methods

They analyzed the most common hereditary metabolic diseases (HMD): phenylketonuria (PKU), congenital hypothyroidism (CH), adrenogenital syndrome (AGS), cystic fibrosis (CF) and galactosemia (GAL). In order to analyze the incidence rates among the Belgorod region population (21 districts), the birth rate data were obtained for the period from 2006 to 2013 (the data from the statistics department of the Belgorod region) and the data on the number of children born with a hereditary metabolic pathology (the data from the regional medical genetic consultation).

Results and Discussion

They began to introduce neonatal screening for PKU and congenital hypothyroidism on the territory of Belgorod region since 1984 with medical genetic consultation, and in 2016 they included galactosemia, adrenogenital syndrome, and cystic fibrosis to the screening program.

Phenylketonuria is monogenic, autosomal recessive disorder, the most common among HMD from the group of aminoacidopathies. According to the mass screening of newborns in different countries the frequency of PKU makes 1: 10,000 on average, but varies considerably depending on population (from 1:4500 in Ireland to 1:10,000 in Finland, and it was not revealed among the Polynesians). The prevalence of PKU in Russia is 1 case per 7000-10000 of newborns. During the period from 2006 to 2013 they recorded 17 cases of PKU among 133134 infants of the Belgorod region (Table 1). The frequency of PKU among the newborns of the Belgorod region makes 1:7831 on the average, which is comparable with the data for Russia. The maximum number of PKU patients in the Belgorod region was recorded in 2006, as well as in 2012 and 2013 (3 cases each). There were no cases of PKU children in 2010 (Table 1). The analysis of PKU territorial distribution in the regional populations of the Belgorod region showed that the maximum values of PKU frequency during the study period were noted in Valuisky (1: 1862), Borisovsky (1:2322), Krasnogvardeisky (1:3015), Rakityansky (1:3221) districts, the minimum ones were recorded in Starooskolsky (1:23051), Belgorod (1:8261) and Shebekinsky (1:7308) districts. In other areas no PKU cases have been reported during the period of 2006-2013. They established the relationship between PKU incidence and the value of random inbreeding, calculated by us earlier [16, 17], among the Belgorod region population. Spearman correlation coefficient between PKU frequency and subdivision level was $\rho = 0.5$ ($p < 0.05$).

Table-1: The number of children born with hereditary metabolic disorders among newborn children in the areas of the Belgorod region (206-2013)

Studied populations (rural municipality)	Number of births	PKU	CH	AGS	CF	GAL	f_r*
Alekseevsky	5180		1				0.00028
Belgorodsky	8520	4		2	1	1	0.00003
town of Belgorod	26909	1	5		2	2	-
Borisovsky	1998	1	3				0.00022
Valuisky	5242	3	1	2	1		0.00015
Weidelevsky	1754		2				0.00033
Volokonovsky	2496			1			0.00024
Grayvoronsky	2176			1	1		0.00029
Gubkinsky	8262	2	1	2			0.00019
Ivnyansky	1762		1		1		0.00048
Korochansky	2857		1		1		0.00022
Krasnensky	829						0.00125
Krasnogvardeysky	3015	1			1		0.00025
Krasnoyaruzhsky	1331						0.00052
Novooskolsky	3067						0.00019
Prokhorovsky	2160						0.00039
Rakityansky	2810	1	1		1		0.00029
Ровенской	2073				1		0.00062
Starooskolsky	19905	1	1				0.00007
town of Stary Oskol	17628	2	4			1	
Chernyansky	2731		1				0.00025
Shebekinsky	7308	1	3	1			0.00016
Yakovlevsky	4486		2	1	1		0.00009
Total	133134	17	27	10	11	3	0.00031

Notes: PKU – phenylketonuria, CH – congenital hypothyroidism, AGS – adrenogenital syndrome, CF – cystic fibrosis, GAL–galactosemia

Congenital hypothyroidism is conditioned by complete or partial dysfunction of the thyroid gland. According to the literature, in 80-85% of cases inheritance is sporadic. In the remaining 15-25% of cases, it is inherited by autosomal way and recessively. The mass screening of newborns for CH has been carried out in the Belgorod Region since 1993. Among 133,134 of newborns, 27 were diagnosed with congenital hypothyroidism. The frequency of CH in the region made 1:4930, which corresponds to all-Russian values, for which the frequency makes 1 case among 3500 - 4100 of newborns. The maximum number of patients with CH was registered in the Belgorod region during 2010 and made 5 cases. The maximum frequency of CH during the study period was observed in Borisovsky (1:774), Veidelevsky (1:996), Ivnyansky (1:2035), Shebekinsky (1:2436), Yakovlevsky (1:2583), Korochansky (1:2884), Chernyansky (1:3107) and Rakityansky (1:3221) districts. The minimum frequency of CH was observed in Starooskolsky (1:23051), Gubkinsky (1:9446) and Belgorod (1:8261) areas. No cases of CH were registered in other areas during the period of 2006-2013. Spearman's correlation coefficient between the frequency of CH and the level of division amounted to $\rho = 0.5$ ($p < 0.05$).

Adrenogenital syndrome (AGS) (congenital adrenal hyperplasia, Wilkins syndrome) is THE group of diseases based on THE defect in one of enzymes or transport proteins involved in cortisol biosynthesis of the adrenal cortex. The mass screening of newborns for adrenogenital syndrome has been carried out in the Belgorod region since 2006. This disease is inherited as autosomal recessive type. The frequency of AGS among the newborns of the Belgorod region for the period from 2006 to 2013 was 1:13313. The maximum number of patients with AGS in the Belgorod region was registered in 2006 - 3 cases. There were no cases of children born with AGS in 2008, 2009 and 2011. The maximum frequencies of AGS (1:3369) are observed in Valuisky, Volokonovsky, Grayvoronsky, Gubkinsky, Shebekensky and Yakovlevsky areas, and the minimum ones (1:15653) in Belgorod area. There are no cases of AGS in other areas during the studied period.

Cystic fibrosis (CF) is the hereditary disease characterized by multiple organ disorders, with the primary lesion of endocrine glands, bronchopulmonary and digestive systems, characterized by early manifestation, short life expectancy of patients, the course and prognosis severity. This disease is inherited by autosomal recessive type. During the period from 2006 to 2013 the frequency of CF among the newborns of the Belgorod region was 1: 12103, which is comparable with the data for Russia. The maximum number of patients with CF in the Belgorod region was registered in 2007 — 4 cases, there were no cases of children born with CF in 2006 and 2011. Over the past eight years, Greivoronsky, Ivnyansky, Korochansky, Krasnogvardeisky, Rakityansky and Rovensky districts are characterized by the maximum values of CF frequency (1:2354), and Belgorod, Valuysky and Yakovlevsky districts are characterized by the lowest values of CF frequency (1:10417). No cases of CF were registered in the remaining areas during the study period.

Since 2006 they have been conducting the screening of newborns for galactosemia (GAL) in the Belgorod region. Galactosemia is the hereditary disease caused by enzyme system defect involved in galactose metabolism, accompanied by the accumulation of abnormal carbohydrate metabolism products in a body causing severe damage to liver, nervous system, eyes and other organs. This disease is inherited by autosomal recessive type. The frequency of GAL was 1:33284 among the newborns of the Belgorod region during the period from 2006 to 2013. The maximum frequency of GAL (1: 13769) is in the Belgorod district, and the minimum one (1:23051) is in the Starooskolsky district. No cases of GAL were recorded in the remaining areas during the study period.

Conclusion

Thus, 58 newborns with hereditary metabolic diseases (phenylketonuria, cystic fibrosis, congenital hypothyroidism, adrenogenital syndrome, galactosemia) needing appropriate pharmacotherapy have been identified after the study in the Belgorod region from 2006 to 2013. The frequency of PKU, CH, CF and GAL among the newborns in the region is comparable to the average Russian data, while the frequency of AGS is lower than in Russian populations and comparable to the frequencies of the European population.

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