The multifactorial model of inheritance of infantile hypertrophic pyloric stenosis for the Georgian population

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Abstract

Background: Infantile hypertrophic pyloric stenosis (IHPS), characterized by hypertrophy of the pylorus smooth circular muscle layer, is the most common cause of gastric outlet obstruction in infancy and the most common abdominal condition requiring surgery in the first few months of life. In the case of timely surgical intervention, the disease is easily cured; however, with delayed treatment, the pathology is often the cause of perinatal mortality. Thus, it is critically important to determine and predict the risk of the disease.
Aim: The aim of the study was to select the type of hereditary transmission of infantile hypertrophic pyloric stenosis and the distribution model of disease susceptibility, as well as to determine the specific share of genetic and environmental factors in the etiopathogenesis of congenital pyloric stenosis, taking into account the peculiarities of the Georgian population.
Methods: The examination of 52 subjects from the Georgian population with infantile hypertrophic pyloric stenosis and their relatives of I, II, III degrees of kinship (959 persons) was performed. Additionally, 150 control subjects and their relatives of I, II, III degrees of consanguinity (2557 persons) from the total population of Georgia were examined. Screening of probands was carried out by the method of single registration. Examinations were conducted using clinical, genealogical, genetic, and epidemiological methods. Analysis of clinical material was carried out by genetic-mathematical methods, including segregation analysis, genetic correlations, and decomposition of general phenotypic variance into components.
Results: The type of hereditary transmission characteristic of the genetic system of congenital pyloric stenosis for the Georgian population is consistent with a multifactorial model with a quasi-continuous distribution of the model.
Conclusions: Within the multifactorial model, in phenotypic dispersion the specific share of genotypic factors determining the difference between individuals is 95.6% (Ga=54.4%, Gd=41.2%), and the systemic environmental factor is Ec= 4.4%.
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Keywords: : Infantile hypertrophic pyloric stenosis, Georgian population, inheritance, multifactorial model.

Introduction

Pyloric stenosis, also known as infantile hypertrophic pyloric stenosis (IHPS), is the most common cause of gastric outlet obstruction in infancy and the most common abdominal condition requiring surgery in the first few months of life (1, 5). Pyloric stenosis is characterized by hypertrophy of the pyloric smooth circular muscle layer. Because the stomach opening becomes blocked, leading to an inability to pass food from the stomach into the duodenum, (2) babies start vomiting, and serious problems such as dehydration and loss of minerals (potassium and sodium), hypochloremic, hypokalemic metabolic alkalosis as well as weight loss, develop. Mortality was high (50%) until successful treatment by pyloromyotomy was developed by Ramstedt in 1911 (2). In the case of timely surgical intervention, the disease is easily cured. Although advances in medical knowledge and care have resulted in minimal mortality and morbidity today, the cause of IHPS remains unclear (8, 9, 10, 13, 14, 15).

The association of IHPS with genetic and environmental factors has been shown (8, 10, 11, 15). Familial aggregation has been described, and a family history is seen in 47.9 % of siblings (3, 14). Although IHPS is highly heritable (Krogh et al. 2010; Fadista et al. 2019), it is a complex disease that does not have Mendelian transmission through families. Multifactorial or polygenic inheritance is the most satisfactory explanation for the observed distribution pattern (4,10, 11). According to this interpretation, multiple genetic (Fadista et al. 2019; Feenstra et al. 2013; Feenstra et al. 2012) and environmental factors (Lund et al. 2014; Krogh et al. 2012a; McAteer et al. 2013; Krogh et al. 2012b; Zhu et al. 2017) operate together to produce infantile hypertrophic pyloric stenosis (4, 13, 15).

The incidence of HPS is higher in non-Hispanic white

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males, firstborns, preterm births (<37 weeks) and infants from multiple gestations (16). There is, however, a variation in the incidence of HPS in the Africans, which varied from 1/5500 to 12.9/10,000 children. The reported incidence of 1/5500 live births in Tanzania was considerably lower than trends seen in other parts of the world (16).

This worldwide disease is more common in Caucasians and probably on the increase (6). The incidence of HPS in the Caucasian population is 5/1000 newborns compared to the African population in which it is rarer. In the United States of America, the frequency in white children is 0.13 % of the total live births (16).

Further studies on different populations, the general population, and familial segregation to determine the prevalence, influence, and mode of familial aggregation and correlation with environmental factors are needed to determine the etiology of IHPS (3). There are no data about the role of environmental factors and genetic-population parameters of infantile hypertrophic pyloric stenosis in Georgia. Therefore, the aim of the present study was to select the type of hereditary transmission of IHPS and the distribution model of disease susceptibility, as well as to determine the specific share of genetic and environmental factors in the etiopathogenesis of congenital pyloric stenosis, considering the peculiarities of the Georgian population.

It can be organic (pituitary, hypothalamic) and idiopathic, as well as secondary, among which primary hypothyroidism occupies an important place(2,3). Secondary hyperprolactinemia occurs in 30% of patients with primary hypothyroidism(4).

Study of the impact of hypofunction of thyroid gland on the functioning of reproductive system is still of great medical interest. Causes of folliculogenesis disorders in the ovaries during hypothyroidism are not yet fully studied. Some researchers explain reproductive dysfunction during primary hypothyroidism with secondary hyperprolactinemia, however, it should be mentioned that increase of prolactin levels in the blood during hypothyroidism is not always observed(5,6).

Increase in thyrotropin-releasing hormone (TRH) is considered to be the cause of development of secondary hyperprolactinemia on the background of primary hypothyroidism(7). Hyperproduction of prolactin has been linked to increase in thyroliberin levels and increase in the susceptibility of lactotrophs on its impact. Hyperprolactinemia causes inhibition of luteinization of follicular granulosa cells and steroidogenesis in the ovaries, which in turn leads to reproductive disorders(8-10).

There are three types of hyperprolactinemia: mild hyperprolactinemia, where prolactin level varies from 25 to 50 ng/ml; moderate hyperprolactinemia, where prolactin level is 50-100 ng/ml and higher prolactin levels >100 ng/ml.

Examination of thyroid gland function has great importance for the treatment of etiopathogenetically justified treatment of hyperprolactinemia, since the treatment and outcome of the treatment of hyperprolactinemia depends on the underlying cause(2,11,12). Hyperprolactinemia developed on the background of primary hypothyroidism is eliminated by hormone replacement therapy with thyroid drugs(8,2,13). In case, when, despite stable compensation of hypothyroidism, this treatment does not normalize prolactin levels, inclusion in the treatment regimen of dopamine agonists in combination with thyroxine is considered (10).

Numerous performed clinical studies have shown that abnormal levels of prolactin and thyroid hormone in blood serum are associated with fertility disorders(14-17) In addition, there is an opinion that not only abnormal prolactin and thyroid hormones indicators, but also a certain ratio between them contribute significantly to female infertility(18).

Given all of the above, study of the link between hyperprolactinemia and thyroid gland hypofunction, as well as determination of the effects of treatment in women with reproductive disorders during hyperprolactinemia developed on the background of primary hypothyroidism is of great medical importance, which led us to the implementation of the present study.

Aim of the study was to determine effectiveness of performed treatment with thyroxine in women with hyperprolactinemia developed on the background of primary hypothyroidism, determination of correlations between prolactin and other hormones before and after treatment in women with hyperprolactinemia developed on the background of primary hypothyroidism.

Methods

The basis of the study is the examination of 52 subjects from the Georgian population with congenital pyloric stenosis and their relatives of I, II, III degrees of kinship (959 persons). Also, 150 control subjects and their relatives of I, II, III degrees of consanguinity (2557 persons) from the total population of Georgia were examined. Screening of probands was carried out by the method of single registration. Examinations are carried out by both clinical (anamnesis, examination, X-Ray, etc.) and genealogical as well as genetic, and epidemiological methods.

Ethical consent

Each participant was asked to sign a written ethical consent during the questionnaire interview.

Data analysis

Analysis of clinical material is carried out by genetic-mathematical methods, including segregation analysis, genetic correlations, and decomposition of general phenotypic variance into components. (4)

Results and discussion

Genetic determination of congenital pyloric stenosis is indicated by a reliable increase in the disease in relatives of patients compared to controls (Table 1), (Fig. 1). As we can see, the frequency of the disease decreases with the distance of kinship.

To determine the hereditary type of transmission, we performed a segregation analysis. The results of the segregation analysis allowed us to reject the recessive type of transmission (SF=0.035). In the next stage of the work, we

determined genetic correlations between relatives within two main models: monogenic, when the disease is caused by a single gene mutation, and multifactorial, when the disease is caused by the presence of many pathological genes and environmental factors. The data of the genetic-correlation analysis are presented in table 2.

As evident, the genetic correlations between relatives in the monogenic model are not reliable ($t<1.96$), while the correlations in siblings and parents correspond to the multifactorial model with a quasi-continuous distribution of the model. Given that the type of disease transmission aligns with the multifactorial model, where both genetic and environmental factors contribute to the determination of the disease, the quantitative contribution of these factors to the manifestation of the disease is of interest. The breakdown of phenotypic variance into components reveals that the specific share of the additive genetic component is 54.4%, the dominant genetic component is 41.2%, and the systematic environmental factors are 4.4%.

Conclusion

Therefore, the type of hereditary transmission characteristic of the genetic system of congenital pyloric stenosis for the Georgian population is consistent with a multifactorial model with a quasi-continuous distribution of the model. Within this model, the specific share of genotypic factors determining the difference between individuals is 95.6% (Ga=54.4%, Gd=41.2%), and the systemic environmental factor is 4.4%.

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