



CONTENT AND DISTRIBUTION OF HAPTOGLOBIN PHENOTYPES IN CHILDREN WITH CEREBRAL PALSY COMPLICATED BY SYMPTOMATIC EPILEPSY

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Article history:	Abstract:
Received: May 21 st 2021 Accepted: June 6 th 2021 Published: July 7 th 2021	The genetic aspects of the development of various diseases are attracting close attention of researchers. Discussions are underway about the genetic predisposition of an individual to a particular pathology. First of all, this is relevant in the development of hereditary neurological diseases, many of which are manifested in early childhood.
Keywords: Cerebral palsy, childhood disability, pathological process, haptoglobin (Hp).	

THE URGENCY OF THE PROBLEM

The problem of cerebral palsy (cerebral palsy) is extremely relevant due to the high prevalence of perinatal pathology of the nervous system, leading to childhood disability.(1) There is no consensus among specialists in the treatment of various forms of the disease. The very concept of cerebral palsy is collective and includes a number of polyetiological and polymorphic neurological syndromes. In addition, the disease is aggravated by the development of symptomatic epilepsy (SE). But many questions of this combination - the frequency of occurrence, the nature of seizures in various forms of cerebral palsy, diagnosis, pathogenesis, prognosis and treatment of SE are still poorly understood and therefore debatable.(2) In particular, of great scientific and practical interest is the question of why in some cases cerebral palsy is not accompanied by epilepsy, while in others it is aggravated by an epileptic seizure.

There is an assumption that it depends on the nature and localization of the pathological process, on the clinical form of the disease or on a genetic predisposition. The solution to these questions determined the purpose of this study.(4)

Apparently, in cases of persistent progression of the disease, as well as spontaneous improvement in health, a large role belongs to the features of genetically determined defense factors, one of which is haptoglobin (Hp). The inheritance of the types of haptoglobin in strict accordance with the Mendelian distribution, the constancy of their state in individual life and the possibility of a clear and uncomplicated definition made it possible to use this serum protein as a genetic marker.(9-10)

Haptoglobin is polymorphic. The most common are three main genetically determined Hp phenotypes, which are determined by a combination of two allelic genes Hp1 and Hp2: homozygous types Hp1-1, Hp2-2 and heterozygous - Hp1-2. In addition to the main phenotypes of haptoglobin, more than 20 of its rare variants have been described. Many publications indicate the relationship between the type of haptoglobin and the predisposition to a number of diseases. The phenotypes of haptoglobin can be used to identify individuals who are at risk for the formation of certain diseases [6]. However, studies of the types of haptoglobin in children with cerebral palsy complicated by epilepsy are insufficient, and the data presented are very contradictory.

In addition, haptoglobin, along with other "acute phase" proteins, perform a variety of physiological and protective functions [5]. It has been proven, in particular, that serum haptoglobin has protective functions and its content in the blood in pathology can have diagnostic and prognostic significance. The supposed correlative relationship between the Hp variants and the state of the immune status makes it possible to use the definition of the Hp phenotype as one of the elements in diagnosing the susceptibility to diseases.

THE AIM OF THE STUDY

The aim of the study was to elucidate the features of the course of various clinical forms of cerebral palsy without epilepsy and complicated SE, depending on the haptoglobin phenotype.

MATERIALS AND METHODS OF RESEARCH

The study was carried out in the children's neurological department of the Bukhara regional children's multidisciplinary center in 2017 -2020. 138 children aged 1 to 16 years were examined, which made up 3 groups: Group I -49 children with cerebral palsy with SE; Group II - 59 patients with cerebral palsy without SE and group III - 30 healthy children (control group) .The diagnosis was established on the basis of the clinical classification of cerebral palsy by K.A. Semenova, which corresponds to the International Classification of Diseases ICD-10 / ICD-10 No. 7 [43, C.41]. The following forms of cerebral palsy have been established:

- 1 double hemiplegia
2. Spastic diplegia
3. Hemiplegic
- 4.Hyperkinetic
5. Atonic-astatic forms.

Hp phenotypes and its level were determined using UNIMATE 3 HAPT kits, at the Central Scientific Research Laboratory of the Institute of Higher Education according to the attached instructions. Hp was typed in blood serum by the method of diselectrophoresis in PAGE according to the Devis method modified by NA Osina (1982) [138, pp. 37-38]. The method is based on the difference in the electrophoretic mobility of the Hp-Hb complex and free hemoglobin.

There are three genetically determined Hp phenotypes, which are determined by a combination of two allelic genotypes Hp1 and Hp2: homozygous phenotypes Hp1-1, Hp2-2 and heterozygous Hp2-1. These Hp phenotypes have different molecular weights and different electrophoretic mobility. The Hp concentration is constant under physiological conditions. The average level of Hp in the blood does not have significant sex and age differences. A certain difference in the Hp content was noted in different Hp phenotypes.

RESULTS OF THE STUDY:

We found that, in comparison with controls, in children with cerebral palsy, the proportion of homozygous types of phenotypes Hp1-1 and Hp2-2 increases, against the background of a noticeable decrease in the heterozygous one - Hp 2-1 (Table 1).

Table 1
Frequency of occurrence of haptoglobin types in children with various forms of cerebral palsy and complicated SE, %

Group	Hp1-1		Hp2-1		Hp2-2	
	with SE	without SE	with SE	without SE	with SE	without SE
Healthy children (control), n = 30	13,4		50,6		30,0	
Patients with cerebral palsy, n = 108	20,7	19,1	39,6↓	40,2↓	39,6	40,7
hemiplegia, n = 22	27,3↑	28,7↑	18,2↓	19,7↓	54,5↑	51,6↑
double hemiplegia, n = 21	20,0↑	18,8↑	40,0↓	39,8↓	40,0↑	41,4↑
spastic diplegia, n = 24	28,6↑	30,1↑	57,1↑	58,4↑	14,3↓	11,5↓
hyperkinetic, n = 20	9,1	10,2	27,3	29,1	63,6↑	60,7↑

The severity of the indicators depended on the form of cerebral palsy. Thus, in children with cerebral palsy hemiplegia, the frequency of occurrence of the phenotypes of haptoglobin 1-1, 2-1, and 2-2 did not differ from the frequency of healthy children, and double hemiplegia revealed this ratio towards the prevalence of the later homozygous form of haptoglobin: 27.3; 18.2 and 54.5%. Distribution of Hp1-1, Hp2-1 and Hp2-2 in patients with spastic diplegia - 20; 40 and 40%, hyperkinetic - 28.6; 57.1 and 14.3%, and with atonic-astatic form of cerebral palsy - 9.1; 27.3 and 63.6%, respectively.

Consequently, the Hp2-2 phenotype is a risk factor for the development of such severe forms of cerebral palsy as double hemiplegia and atonic-astatic forms. The Hp1-2 phenotype was more often detected in case of double hemiplegia and hyperkinetic form. In our opinion, the presence of the Hp2-1 phenotype in children is favorable for the formation of a healthy generation.

We did not reveal a definite dependence of the frequency of occurrence of phenotypes of haptoglobin on the presence or absence of SE, age, mental retardation.

The peculiarities in the distribution of the haptoglobin phenotype in children with various forms of cerebral palsy are apparently due to their predisposition to the formation of severe forms of cerebral palsy, which indicates the possibility of further formation of a pathological focus and transition to a more severe course. This should be expected, since the mechanism of development of these types of cerebral palsy is different, and is associated with the state of the central mechanisms of regulation. So, the morphological basis of hemiplegia is porencephaly in the area supplied by the middle cerebral artery or cerebral hemiatrophy. The muscle tone in the affected limbs is increased. Necrosis of the periventricular white matter of the brain with the formation of cysts and foci of gliosis often leads to spastic diplegia. In this case, long paths from the cerebral cortex are involved in the pathological process. The fibers going to the legs are closer to the ventricles and the likelihood of their damage is much higher than those lying laterally and going to the arms according to Auerbach-Flatau (eccentric arrangement of long conductors). The hyperkinetic form of cerebral palsy is caused by symmetrical damage to the subcortical structures of the brain. The atonic-astatic form of cerebral palsy is caused by damage to either the cerebellum itself or its connections with the cortex. Severe general brain damage is characteristic of double hemiplegia. With a spastic form, muscle tone changes according to a spastic type, and not due to muscle stiffness, contractures and deformities of the limbs occur, which is associated with stem activity. The hyperkinetic form is characterized by a delay in the reduction of tonic reflexes, the development of set reflexes and voluntary motor skills, while paresis and paralysis are noted at the same time.

It should be noted that the Hp1-1 phenotype is more "ancient" in origin. In the course of human evolution, apparently, a new allele of the Hp2 gene appeared, which determines the appearance of the Hp2-1 and Hp2-2 phenotypes and spread as a result of natural selection. Apparently, carriers of this gene are more resistant than Hp1 to environmental factors. This is confirmed by the high susceptibility of individuals with the Hp1-1 phenotype to liver diseases [7]. We considered it inappropriate to look for a connection between certain phenotypes of haptoglobin and etiological factors in the development of cerebral palsy. Apparently, haptoglobin affects one of the links in the pathogenesis of cerebral palsy.

Haptoglobin reacts to pathology by changing its concentration, so its content can serve as a sensitive test for the physiological state of the body [4]. Interesting results were obtained when studying the level of haptoglobin in the blood serum of children with various forms of cerebral palsy. So, with all forms of cerebral palsy without SE, an increase in its level by 54.4 was revealed; 53.2; 43; 105.1 and 55.7%, respectively, with hemiplegia, double hemiplegia, spastic diplegia, with hyperkinetic and atonic-aesthetic forms of cerebral palsy (Table 2.). Especially increased the content of haptoglobin in the hyperkinetic form of cerebral palsy.

Table 2

The content of haptoglobin in the blood serum of children with various forms of cerebral palsy and symptomatic epilepsy, g / l

Group	with CE	P	without CE	P1	P2
Healthy children (control), n = 30	0,79±0,03				
Patients with cerebral palsy, n = 108	1,49±0,05	<0,001	1,29±0,04	<0,001	<0,001
hemiplegia, n = 22	1,36±0,08	<0,001	1,22±0,05	<0,001	>0,05
double hemiplegia, n = 21	1,38±0,13	<0,001	1,21±0,04	<0,001	>0,05
spastic diplegia, n = 24	1,44±0,13	<0,001	1,13±0,03	<0,001	<0,001
hyperkinetic,	1,80±0,11	<0,001	1,62±0,05	<0,001	>0,05
	1,38±0,07	<0,001	1,23±0,03	<0,001	<0,001

In patients with cerebral palsy with SE, a more pronounced increase in the level of haptoglobin was found: by 72.1; 74.7; 82.3; 127.8 and 74.7%, respectively, hemiplegia, double hemiplegia, spastic diplegia, hyperkinetic and atonic-astatic forms of cerebral palsy. The greatest increase in the level of haptoglobin was also characteristic of the hyperkinetic form of cerebral palsy. Significant excess of the Hp level in children without SE was noted only for spastic diplegia. There were no differences depending on age.

Apparently, this is due to the fact that haptoglobin belongs to the acute phase proteins, and an increase in its content is usually associated with the development of an inflammatory reaction. Haptoglobin is able not only to bind hemoglobin, forming a complex with spheroidase activity, but rather effectively inhibit cathepsins C, B, and L. In addition, its participation in the utilization of some pathogenic bacteria has been established; therefore, it is assumed that it can be used in the treatment of certain infections. Increased consumption of haptoglobin, C3 component of complement, fibrinogen may indicate another pathological process accompanying inflammation [6].

Indeed, for children with cerebral palsy, in addition to the underlying disease, concomitant diseases and pathological conditions are diagnosed - protein deficiency, hypochromic anemia, calciopenic vitamin deficiency states, lesions of the gastrointestinal tract, etc.

In patients with cerebral palsy and complicated SE, Hp activity also depended on the phenotype. Thus, in these children with hemiplegia and double hemiplegia, the activity of Hp1-1 exceeded the indices of other phenotypes. At that time, in spastic diplegia, the activity of the Hp1-1 and Hp2-1 phenotypes was higher than that of the Hp2-2 phenotype. The level of the latter was the lowest than in the other groups. In hyperkinetic cerebral palsy, the activity of Hp1-1 and Hp2-1 was the highest, and the priatonic-aesthetic activity of Hp1-1 was the lowest.

We established the presence of concomitant infectious and inflammatory diseases. Depending on the climatic season, children often suffered from ARVI. In contrast to the general population, their disease was protracted, with a transition to a chronic form. It should be especially noted that the presence of SE further aggravated the condition of the patients. They were more immune-compromised, resistant to pharmacotherapy; some lag in their physical development was noted. Taking into account the role of haptoglobin in the development of immune reactions, the influence of an increased level of haptoglobin in patients with cerebral palsy with SE is of great interest.

Thus, we found that in children with cerebral palsy, depending on the form, the content of the Hp1-1 phenotype increases. The Hp2-2 phenotype is more frequent in patients with double hemiplegia and atonic-astatic form. The predisposition of the Hp2-2 phenotype to the development of these forms in children with cerebral palsy is associated with the peculiarities of dysregulation of central mechanisms and determines the possibility of the subsequent formation of a pathological focus and clinical symptoms. In children with cerebral palsy, the level of haptoglobin increases in the blood serum, more pronounced in the hyperkinetic form.

It should be borne in mind that the risk of developing one form or another of cerebral palsy depends on the phenotypic signs of haptoglobin: the Hp2-2 phenotype is most often detected in patients with double hemiplegia and atonic-astatic forms. Possible transformation of atonic-astatic form of cerebral palsy into spastic, more severe - double hemiplegia. Adequate pathogenetic antispastic therapy and habilitation measures should be carried out in a timely manner.

Children with cerebral palsy are often exposed to various diseases, which often lead to their death. For the prevention of these conditions in frequently ill children, the content of haptoglobin should be determined for timely treatment.

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