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The Use of Cytoflavin in the Complex Treatment of Neuroinfections in Children

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We present here results obtained from the use of Cytoflavin in the complex treatment of bacterial purulent meningitis and viral encephalitis in 60 children aged from one month to 18 years. Cytoflavin was shown to be clinically effective, decreasing the incidence of residual signs and shortening recovery periods. Cytoflavin was also found to have influences on endothelial dysfunction, the rheological properties of the blood, the clotting system, and vascular tone. The use of Cytoflavin in the complex pathogenetic treatment of neuroinfections in children is recommended.

Keywords: children, neuroinfections, meningitis, encephalitis, endothelial dysfunction, Cytoflavin.

One of the most important areas in the structure of infectious diseases is occupied by infections of the central nervous system (CNS), which are characterized by severe courses, high mortality (8–36%), and frequent residual sequelae affecting the nervous system (26–75%). Despite significant advances in the study of pediatric infections, mortality from neuroinfections remains high and organic CNS disorders during the residual period are seen in almost half of the children falling ill. Thus, increases in the efficacy of the treatment of bacterial purulent meningitis (BPM) and viral encephalitis (VE) in children constitute a relevant medical and social problem.

Involvement of vessels and impairments to the hemostasis system are among the major branches of pathogenesis in infectious processes, including those in the CNS, and are not infrequently clinically apparent. Recent years have seen increases in the incidence of cerebrovascular complications of infectious diseases, with occlusion and stenosis of vessels associated with impairments to the rheological properties of the blood; these require studies of the state of vessel walls in infectious processes and improvements in pathogenetic treatment [3, 5].

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Neuroinfections involve generalized damage to vessels, including the cerebral vessels, associated with various pathogenetic mechanisms damaging the endothelium, neural regulation of vessel tone, and impairments to the coagulation component with excessive thrombus formation. Thus, BPM involves a predominance of damage to the endothelium and VE is associated with impairments to its functional activity, with disordered vessel tone. Marked changes in D-dimer levels in VE and circulating leukocytes in BPM, both in the acute phase of disease and during the subsequent 1.5 months, point to the pathogenetic significance of the structural-functional properties of vessel walls in the genesis of neuroinfections in children [7, 8]. This provides the grounds for the differentiated utilization of various vascular preparations in neuroinfections, directed both to normalization of endothelial structure and its function and activity and to correcting vessel tone. Considering the different extents of vascular changes, treatment in neuroinfections must also be differentiated. Thus, neuroinfections, particularly in children, the timely prescription of vascular preparations is a vital part of pathogenetic therapy.

Given that pediatric practice involves a preference to avoid agents with complex actions, the use of a single combined formulation with multifactorial actions is recommended. One such Russian agent is the complex formulation Cytoflavin. Containing succinic acid, riboxin, nicotinamide, and riboflavin mononucleotide sodium, Cytoflavin has

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TABLE 1. Durations of the Main Clinical Symptoms (days) in Children with BPM and VE Depending on Therapeutic Tactics

Clinical symptom	BPM		VE	
	study group (n = 30)	reference group (n = 30)	study group (n = 30)	reference group (n = 30)
Severe state	3.1±0.2*	5.3±0.5	4.0±0.8*	6.3±1.0
Duration of elevated temperature	4.0±0.5*	5.9±0.6	2.3±0.4*	4.5±0.7
Impaired consciousness	1.8±0.4*	4.3±0.6	2.0±0.9*	6.0±0.3
Intoxication syndrome	3.8±0.1*	6.2±0.3	4.3±0.9 *	7.6±0.8
General cerebral symptomatology	3.5±0.3*	5.6±0.5	2.8±1.0*	6.0±2.3
Focal symptomatology	2.1±0.3*	4.2±0.7	16.6±2.3*	27.8±4.9
Meningeal symptoms	7.1±0.4*	12.0±1.9	3.2±0.2*	5.0±0.9
CSF changes	10.7±1.5*	14.5±1.7	3.2±1.1*	7.2±2.3
In-patient days	18.6±1.4*	23.7±3.2	25.3±1.9*	34.9±4.0

Note. Here and in Tables 2 and 3: significant differences at $*p \le 0.05$.

antioxidant and antihypoxic actions, with positive effects on energy formation in cells, decreasing free radical production and restoring enzyme activities. Cytoflavin activates the redox enzymes of the respiratory chain in mitochondria and macroergic compound resynthesis, and facilitates glucose and fatty acid utilization. The formulation has anti-ischemic actions, improves coronary and cerebral blood flow, limits necrosis zones, improves metabolic processes in the CNS, restores consciousness, and reverses reflex impairments and disorders of sensation [1].

Published data indicate that Cytoflavin is recommended for the treatment of serious forms of meningitis in adults, during the acute period of ischemic stroke, the complex treatment of migraine, and asthenoneurotic syndrome, and has immunotropic effects [1, 2, 4, 6, 9–11].

The aim of the present work was to study the therapeutic efficacy and safety of Cytoflavin in the complex treatment of BPM and VE in children.

Materials and Methods

A total of 120 patients with neuroinfection pathology were studied: 60 with BPM and 60 with VE; patients were aged from one month to 18 years and were randomized into two groups. Depending on the nosology and etiology of neuroinfections, all patients received standard treatment: antibacterial (penicillins or third-generation cephalosporins) in BPM or antivirals (Zovirax or Amixin) in VE, along with dehydrating agents (Lasix, Diacarb) and neurometabolites (Pantogam or Gliatilin) for one month.

On the day of admission, patients of the experimental group (n = 60), consisting of 30 patients with BPM and 30 with VE, received initial infusions of pathogenetic treatment consisting of Cytoflavin at a daily dose of 0.6 ml per kg body weight diluted in 100 ml of physiological saline once daily for five days. The reference group (n = 60) consisted of 30 patients with BPM and 30 with VE and received initial infusion therapy consisting of physiological saline at a dose of 10 ml/kg once daily for five days; these patients did not receive pathogenetic infusion treatment.

Treatment efficacy was assessed in terms of the following clinical and laboratory criteria: time to normalization of body temperature, measured in the morning and evening; the duration of general cerebral symptomatology; the duration of intoxication syndrome; the duration of meningeal syndrome; and time to clearing of the cerebrospinal fluid (CSF).

The following laboratory parameters were evaluated: clinical blood investigations on admission and on days 5–6 and 10–11 of treatment; D-dimer and circulating serum endotheliocytes on admission and on days 20–21 and 42–45 from admission.

Data were analyzed statistically using the nonparametric Student's t test. Statistically significant differences were identified at $p < 0.05$.

Results

Clinical analysis of the results obtained by including pathogenetic therapy in the complex of therapeutic measures in patients with BPM and VE demonstrated its efficacy. Injections of Cytoflavin were tolerated well by the patients, with allergic reactions in only two patients; the duration of clinical symptoms in the experimental group was significantly shorter than that in the reference group (Table 1).

Blood inflammatory marker levels decreased on the background of etiological and pathogenetic treatment simultaneously with clinical symptoms (Table 2).

In BPM, normalization of clinical blood tests occurred twice as quickly (12.3 ± 1.2 days) in the group of children receiving treatment including Cytoflavin as in the reference group (20.4 ± 3.5 days). The numbers of circulating serum endotheliocytes by days 20–21 in both groups were greater than normal, though values in the group of children receiving treatment including Cytoflavin were 1.4 times lower (6.6 ± 0.3 compared with 8.3 ± 1.4 cells/μl). By day 42–45, endothelial desquamation in the experimental group approached normal (5.7 ± 0.2 cells/μl), while even by day 45, numbers of circulating endotheliocytes in the reference

TABLE 2. Duration and Dynamics of Changes in Clinical Blood Test Results in Children with BPM (n = 60)

Laboratory parameter	Study group (n = 30)			Reference group (n = 30)		
	days 20–21	days 42–45	duration of changes (days)	days 20–21	days 42–45	duration of changes (days)
Leukocytes ($\times 10^9$/liter)	7.3±1.2*	6.4±1.7*	12.3±1.2*	12.3±2.4	8.3±1.2	20.4±3.5
Circulating endotheliocytes (normal: less than 4 cells/μl)	6.6±0.3*	5.7±0.2*	42.7±2.5*	8.3±1.4	6.4±1.2	45.0±3.8
D-dimer (normal: 150–550 μg/liter)	500.6±100.3*	468,9±62,5*	20.5±1.3*	1250.8±175.0	436.1±74.8	43.0±4.8

TABLE 3. Duration and Dynamics of Changes in Clinical Blood Test Results in Children with VE (n = 60)

Laboratory parameter	Study group (n = 30)			Reference group (n = 30)		
	days 20–21	days 42–45	duration of changes (days)	days 20–21	days 42–45	duration of changes (days)
Leukocytes ($\times 10^9$/liter)	6.6±1.2*	6.7±0.9*	5.6±1.9*	7.2±0.9	6.9±1.0	11.1±4.9
Circulating endotheliocytes (normal: less than 4 cells/μl)	4.3±0.3*	4.0±0.2*	21.0±2.9*	5.0±0.5	4.2±0.6	32.9±4.9
D-dimer (normal: 150–550 μg/liter)	1001.0±111.1*	652.2±43.8*	45.9±2.8*	1450.0±125.3	850.0±95.7	75.0±4.8

group were greater than normal (6.4 ± 1.2 cells/μl). Vascular therapy including Cytoflavin led to normalization of serum D-dimer by day 20–21 in the experimental group, while the level decreased only by day 42–45 in the reference group.

In VE, patients in the experimental group showed normalization of clinical blood tests two times as quickly as the reference group (5.6 ± 1.9 and 11.1 ± 4.9 days, respectively). Treatment including Cytoflavin produced normalization of circulating endotheliocytes by 20–21 days in the experimental group, to a level of 4.3 ± 0.3 cells/μl, while the level in the reference group at three weeks from the start of treatment showed only a minor reduction, to 5.0 ± 0.5 cells/μl. Serum thrombus formation marker levels in both groups were greater than normal by day 20–21 of the study in both groups, though the group of children receiving traditional treatment had a level 1.5 times higher than that in the experimental group (1450.0 ± 125.3 and 1001.0 ± 111.1 μg/liter, respectively). D-dimer levels remained elevated in both groups by day 42–45, though patients in the experimental group receiving treatment including Cytoflavin had significantly lower levels (652.2 ± 43.8 and 850.0 ± 95.7 μg/liter, respectively) (Table 3).

Disease outcomes in the experimental group of children with BPM showed complete recovery in 83% of cases, with complete recovery in 77.8% of patients with VE; in patients of the reference group, outcomes were dominated by neurological deficit, not infrequently including severe (up to 55%). Thus, inclusion of Cytoflavin in the complex treatment of both BPM and VE, which has multifactorial actions, not only decreased the duration of the main syndromes of neuroinfection and accelerated normalization of laboratory values, but also decreased the proportion of cases with neurological deficit and shortened in-patient duration.

Discussion

The present studies showed that the early use of the complex formulation Cytoflavin in the pathogenetic treatment in the acute period of BPM and VE promotes reductions in the duration of the main clinical symptoms of disease. This effect would appear to be associated with the multifactorial actions of Cytoflavin, primarily its ability to improve cerebral circulation, activate metabolic processes in the CNS, and restore sensation and cognitive-mnestic brain functions. Given that in neuroinfections, neuron damage and repair occur simultaneously, it is possible that the early use of Cytoflavin has neuroprotective actions [10]. Normalization of clinical blood tests in the experimental group over short time periods also provides evidence of the anti-inflammatory effect of Cytoflavin, perhaps due to activation of metabolic processes and inhibition of proinflammatory cytokine synthesis [11–13]. In addition, use of Cytoflavin led to rapid normalization of circulating endotheliocyte and D-dimer levels evidencing structural-functional damage to the endothelium. This pattern of changes is probably associated with the ability of Cytoflavin to improve blood rheological properties, thus producing an indirect angioprotective effect. In the reference group, where Cytoflavin was not used – physiological saline was used alone for detoxification – the persistent increases in endotheliocytes and D-dimers were probably linked with the prolonged persistence of endothelial dysfunction and structural vascular changes.

Thus, in BPM and VE in children, the use of the complex formulation Cytoflavin as initial pathogenetic infusion treatment is highly effective. Good clinical tolerance and safety were seen with Cytoflavin; the only side effect on infusion of Cytoflavin was allergic rash in 3.3% of

patients. Cytoflavin not only had anti-inflammatory and neuroprotective actions, but also improved the rheological properties of the blood. Thanks to improvements in the treatment of BPM and VE in children, use of infusions of the pathogenetic substance Cytoflavin shortened the inpatient stays of children by an average of seven days and decreased the incidence of residual neurological deficit from 35% to 15%.

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