Original Article

Acute Approach to Central Nervous System Infections in Kazakhstan

Yerzhanova Akmaral[1], Kemelbekov Kanatzhan[1], Ayaganov Dinmukhamed[2], Seitkhanova Bibigul[1], Ospanova Elmira[3], Sarsenbayeva Gulzat[1], Seidakhmetova Aizat[1], Kylyshbekova Gulzhamal[3]

ABSTRACT

Background

Neuroinfections in children are a socially significant problem of our time, as they can lead to disability and death of the patient, which actualizes the need for their early clinical diagnosis. The purpose of the study: to identify patterns of clinical manifestations of central nervous system lesions in children with neuroinfections.

Materials and methods

The cases of neuroinfections in 101 children treated at the "City Clinical Infectious Diseases Hospital" (Shymkent) in the period from 2018 to 2022 were analyzed, of which 37 patients with viral neuroinfections, 64 with bacterial ones.

Results

The predominance of bacterial neuroinfections over viral ones was revealed, with a predominance among young boys. Headache or its equivalents (in children under one year old) were observed in 72.5%; most often in children with viral infections of the nervous system (81.2%), less often in patients with bacterial infections (65.4%), p 0.01. In most cases, the disease manifested with the phenomena of fever and vomiting. When assessing the neurological status, the duration of preservation of two frequently occurring meningeal signs (rigidity of the occipital muscles, Kernig's symptom) was taken into account, which was 6 ± 1.3 days and 5 ± 1.1 days in the group with bacterial neuroinfections, and 4 ± 1.8 and 5 ± 1.7 days, respectively, in the group with viral neuroinfections (p 0.05). With pneumococcal etiology, the most severe and protracted cases of the course of neuroinfections are recorded. Frequent emergency conditions in infectious lesions of the central nervous system in the form of cerebral edema, septic shock, which occur more often in bacterial neuroinfections, have been identified.

Conclusion

Neuroinfections are characterized by a symptom complex of clinical manifestations, which should be interpreted by doctors in a timely and correct manner in order to diagnose early and minimize adverse outcomes of the disease.

Keywords

infections, central nervous system, clinical manifestations, children

INTRODUCTION

Neuroinfections refer to a group of infectious diseases that primarily affect the central nervous system (CNS), leading to specific clinical symptoms. These infections are particularly severe because they often progress quickly, leading to complications and high mortality rates[1,2,3,6]. Children with bacterial neuroinfections (BNI), especially those suffering from hypertoxic forms of meningococcal infections, face the highest risk of complications and death, even though overall infection rates remain low[5,6,7,10]. However, in some areas, lower mortality rates are observed, likely due to early diagnosis and effective treatment that help prevent and manage complications[8].

In the structure of infectious morbidity, meningococcal infection (MI) is one of the life-threatening and unpredictable in terms of lightning speed. The highest incidence rate is observed in the so-called "meningitis belt", which stretches across Africa from Senegal to Ethiopia and covers 26 countries[11]. Of the currently known 13 serological groups of Neisseria meningitidis, only three of them – A, B, C – are responsible for more than 90% of generalized forms of MI. Meningococcus is the main cause of meningitis, a rapidly developing septicemia

1. South Kazakhstan Medical Academy, Kazakhstan, Symkent
2. West Kazakhstan Marat Ospanov Medical Univercity, Kazakhstan, Aktobe
3. Khoja Akhmet Yassawi International Kazakh-Turkish University, Kazakhstan, Turkistan

Correspondence
West Kazakhstan Marat Ospanov Medical Univercity, Kazakhstan, Aktobe

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and is a public health problem in most countries. Since the introduction of the conjugated vaccine against serogroup A meningococcus (2010), their share in the structure of diseases has sharply decreased, while there is an increase in the circulation of serogroup C and W meningococci. Serotypes of meningococci have features of geographical distribution, so in African countries it is serogroup A; in the USA – B, C, Y, W; in Europe, meningococci of serogroup B have been registered for the last 20 years; In Kazakhstan, there is a circulation of serogroups A, B and C, W with a predominance of serogroups A and B[12].

In Kazakhstan, from 1998 to 2018, the incidence of MI tends to decrease and in long-term dynamics is characterized by cyclicity with an increase in morbidity every 3-4 years[13]. In comparison with the indicator of 2017, in 2018 there was an increase in the incidence of 1.53 times (0.35 and 0.53 per 100 thousand population, respectively). Among the cases, children under 14 years of age accounted for 40.6%; in the age category of 15-19 years and 20-29 years, the incidence was recorded in 20.8% of cases; 13.5% of cases occurred at the age of 30-39 years. "Organized" children were sick more often in comparison with "unorganized" (14.6%) children, 2 cases of diseases were detected among teachers. MI is still characterized by an acute onset with a high temperature that does not decrease after the use of antipyretics, meningeal signs develop rapidly. In recent years, there has been a change in the nature of the rash, which makes it difficult to diagnose MI at the pre-hospital stage, and doctors referred such patients to the hospital with a different diagnosis. In the overwhelming majority of cases (89.6%), meningococcal infection occurred in a generalized form; meningococcemia was diagnosed in 33.3% of patients; meningitis – 11.4%; meningoencephalitis – 4.3%[14,17].

It should be noted that in maintaining the epidemic process of MI, the so-called "healthy" bacterial carriers are of epidemiological importance, the number of which can increase up to 25% in epidemic situations. In 2018, 10.4% of people with nasopharyngitis were identified. Isolated cultures of meningococci are represented by serogroups A – 38.6%; B – 22.8%; C – 10%; X, W were isolated in 4 cases, and meningococci were serologically untyped in 17.18%. According to the National Calendar of Preventive Vaccinations for epidemic Indications, children and adults in the foci of MI are subject to vaccination. Polysaccharide and conjugated meningococcal vaccines available on the international market are either bivalent (groups A and C) or tetravalent (groups A, C, Y and W). Meningococci tend to affect certain age groups and the choice of the target population for immunization may vary depending on the epidemiological situation. A vaccine against meningococcal infection "Nimenrik" produced by Glaxo Smith Kline (Belgium) has been registered in Kazakhstan, it is used for active immunization of adults, adolescents and even children aged 6-12 weeks. It should be noted that as a result of the conducted sanitary and anti-epidemic and sanitary-preventive measures, the incidence of MI in Kazakhstan in 2019 decreased to 0.1 per 100 thousand population. An important role in reducing the incidence was provided by immunization, which today has been and remains the only rational approach in the fight against meningococcal infection. clinical diagnostics[11,16,18].

AIM

To identify the features of clinical manifestations of central nervous system lesions in children with neuroinfections.

MATERIALS AND METHODS

We analyzed cases of neuroinfections among children (n = 101) who received inpatient treatment at the City Infectious Diseases Hospital (Shymkent, Kazakhstan) in the period from 2018 to 2022. Criteria for inclusion in the study: children with an infectious lesion of the central nervous system of both sexes with the informed consent of a legal representative. Exclusion criteria: shunt-neuroinfections (37 patients) and a group with bacterial neuroinfections (64 patients) (Table 1).

The group of children with BNI included patients with isolated lesions of the membranes and/or brain matter (n = 35, 1st subgroup) and 24 children with a combination of lesions of the membranes and/or brain matter with septicemia (2nd subgroup). In 20% of cases, the etiology of isolated lesions of the membranes and/or brain matter was established, the disease was equally often associated with Neisseria meningitidis (28.6%), Haemophilus influenzae b (28.6%), Streptococcus pneumoniae (28.6%), association of Neisseria meningitidis and Streptococcus pneumoniae (14.2%). In 80%, the etiology of the isolated lesion of the membranes and/or the substance of the brain could not be established. In the second subgroup, most diseases are associated with meningococcus (91.7%, 22 cases),

Table 1. Clinical characteristics of the groups (Me ± SD)

Group	Age,months			Gender, abs. (%)	
	General	Girls	Boys	Girls	Boys
Viral neuroinfections (n = 37)	78 ± 24,4	96 ± 25,6	78 ± 21,1	12 (37,5 %)	20 (62,5 %)
Bacterial neuroinfections (n = 64)	17 ± 9	16 ± 6,8	14,5 ± 7,2	25 (42,4 %)	34 (57,6 %)

in two cases the etiological cause of septicemia with meningitis has not been verified.

Non-poliomyelitic enteroviruses (93.7% of patients) were the etiological agents of VNI Coxsacks A9, B2, B4, ESNO6. In 2 cases (6.3%), it was not possible to establish the etiology of viral neuroinfection, but these patients were grouped into a general group of patients with enterovirus infection based on the presence of typical clinical, laboratory and epidemiological signs characteristic of this disease.

The obtained results were statistically processed in accordance with the recommendations on the processing of biomedical research data[12]. Statistical data processing was performed using the BIOSTAT program. Median (Me) and standard deviations (SD) were determined to describe the distribution of quantitative features. The statistical significance of the differences between the two independent populations was assessed using the Mann–Whitney criterion. The differences in the indicators were considered statistically significant at $p \leq 0.05$. For the analysis of groups by a qualitative binary feature, the criterion $\chi 2$ (Pearson) was used.

RESULTS AND DISCUSSIONS

We found that in the period from 2018 to 2022, bacterial lesions of the central nervous system (64.8%) prevailed in the structure of neuroinfections in the Trans-Baikal Territory, which contradicts official statistics, according to which viral meningitis accounts for up to 75% of all neuroinfections[11] and is due to the epidemic rise in the incidence of meningococcal infection in the city of Shymkent in 2018 In the etiological structure of BNI, the leading cause of their development was N. meningitidis (42.4%), especially when the nervous system is affected in combination with meningococcemia. Clinical forms of meningococcal infection among children were characterized by the predominance of a combination of meningococcemia and meningitis (56.4%), the proportion of which, according to the literature, can reach up to 100%[8, 19]. Three cases of mixed forms of meningococcal infection resulted in death due to the fulminant course of the disease and refractory septic shock to therapy. Isolated sepsis (meningococcemia) was observed less frequently in clinical forms of invasive meningococcal infection (15 patients, 38.5%), as well as isolated meningitis (2 patients, 5.1%).

The lesion of the central nervous system is clinically associated with meningeal syndrome, the concept of which includes subjective disorders and objective symptoms detected during examination of the patient. The cardinal meningeal symptom is headache, characterized by significant intensity, diffusivity and a feeling of bursting; this symptom is noted in 90-100% of patients, regardless of the etiopathogen[1, 2, 7, 16, 19]. Headache or its equivalents (in children of the first year of life) in our study was observed in 67 out of 91 patients (73.6%), this symptom was most often found in children with IUI (28 children, 87.5%), in patients with IUI less often (39 children, 66.1%) (p 0.01).

Headache with neuroinfections is almost always accompanied by nausea and often vomiting, which is not associated with eating, occurs suddenly and is recorded from 28% to 80% of cases of the disease, both viral and bacterial etiology[1, 6, 7, 16, 20]. The phenomena of vomiting at fever height, that is, of central genesis, were observed in both groups of patients with a fairly high frequency, but with IUI, this clinical manifestation was detected in 23 children, which was 71.8%, against 37 children from the group with BNI (62.7%) ($p < 0.05$). With neuroinfections of viral etiogenesis, vomiting was observed mainly in boys aged 3 to 11 years (16 people, 55.2%), with bacterial disease in children under 3 years (28 children, 75.6%) ($p \leq 0.01$), regardless of gender. Vomiting as the leading manifestation of the disease was found in the BNI subgroup in children with isolated lesions of the membranes and/or brain matter (24 patients, 64.9%) (p 0.05), compared with the second subgroup. Nausea and vomiting in patients with

an infectious lesion of the central nervous system may be accompanied by abdominal pain, while diarrheal syndrome is observed in a third of patients[7]. In our patients, diarrhea was mainly observed in 32.2% of cases from the group of bacterial neuroinfections, versus 4 patients (12.5%) with serous meningitis (p < 0.01) without a statistically significant difference in the BNI subgroups. It is worth noting that changes in the nature and frequency of stool, taking into account the age of the patient, were recorded in children of both groups only among young children, which is explained by functional immaturity, high sensitivity to the effects of toxins and microorganisms themselves on the neurovascular elements of the gastrointestinal tract. Fever as an initial sign of neuroinfections, according to the literature, is noted in 50% of cases with an interval of 38.5–39.5 ° C[5, 7, 15, 18]. Fever in patients of the group of viral neuroinfections in our case reached febrile figures (38.6 ± 0.6 ° C), the average duration was 3 ± 1.2 days. In general, the duration of fever in serous meningitis is 4 ± 1 day, and repeated temperature waves are observed in 28% of patients on the 5th-8th day and are associated with the involvement of other organs in the process (carditis, encephalitis)[2]. In the observed patients with bacterial CNS lesion, the temperature response values were 38.9 ± 0.9 ° C, which did not distinguish this indicator from that in viral neuroinfections (p 0.05). However, the period of preservation of hyperthermia in patients from the BNI group was recorded longer than in patients with BNI and amounted to 5 ± 1.4 days (p 0.05), which is a reflection of the pathogen's aggression on a macroorganism with a long-term pronounced inflammatory reaction. One of the leading clinical manifestations of neuroinfections is hypersensitivity to acoustic and photo-irritants, as well as hyperesthesia of the skin[7, 14]. When assessing hyperesthesia, we found that patients with bacterial lesions of the central nervous system were predominantly tactile (26 people, 44%) compared with the group of patients with viral neuroinfections, where hyperesthesia on photo-reflectors was mainly noted (14 people, 43.7%) (p 0.01). Acoustic hyperesthesia was detected with the same frequency in both groups (p 0.05). The bulging and pulsation of the large fontanel in children who had ungrown skull bones was evaluated as a manifestation of hypertension syndrome. In total, we identified 11 people with this clinical manifestation, of which 2 (18.2%) were from the IUI group and 9 (15.2%) were from the BNI group, although when comparing the groups, there was no statistically significant difference in the frequency of registration of this symptom (p 0.05). It was noted that 8 (88.9%) patients with bulging and pulsation of the large fontanel from the group of bacterial neuroinfections were in the subgroup of children with isolated meningitis/meningoencephalitis, on the basis of which it can be assumed that hypertension syndrome is most pronounced with isolated lesions of the membranes and/or brain matter.

With neuroinfections in the neurological status, meningeal signs of varying severity and duration are always recorded, which, first of all, include rigidity of the occipital muscles, Kernig's symptom and varieties of Brudzinsky's symptom[1,6,19]. The frequency of meningeal signs in groups of patients with bacterial and viral etiology of neuroinfections is presented in Table 2.

Table 2. Meningeal symptoms in children with neuroinfections

The symptom	Bacterial neuroinfections (*n* = 64)		Viral neuroinfections (*n* = 37)		P
	absol.	%	absol.	%	
Rigidity of the occipital muscles	48	79,6	29	87,5	> 0,05
Kernig 's symptom	29	47,4	13	37,5	> 0,05
Brudzinsky 's upper symptom	21	33,9	11	31,2	> 0,05
Brudzinsky 's symptom is average	9	13,5	8	21,8	> 0,05
Brudzinsky 's symptom is lower	25	40,6	17	50	> 0,05
Lesage 's Symptom	9	15,2	3	9,3	> 0,05
Meningeal posture	16	27,1	0	0	< 0,01

Consequently, meningeal signs were equally common in both groups, with the exception of a specific meningeal pose ("cop dog"), which was registered exclusively in the group of patients with BNI (p 0.01). At the same time, the duration of meningeal symptoms in the study groups differed, so with BNI, the rigidity of the occipital muscles remained 5 ± 1.7 days, relative to patients with BNI (3 ± 1.4 days, p 0.05), the positive Kernig symptom was 4 ± 1.9 and 3 ± 1.2 days, respectively (p 0.05). The duration of preservation of meningeal symptoms in the group of patients with BNI is directly related to an

increase in the time for rehabilitation from the causative agent of bacterial flora and active restoration of the affected structures of the central nervous system.

Of particular interest is the study of impaired consciousness in patients with neuroinfections. It is known that up to 23% of patients with a hypertoxic form of meningococcal infection have pronounced depression of consciousness upon admission to the hospital[5, 19]. We found that depression of consciousness was observed only in patients with bacterial neuroinfections (copor – 6 people (8.1%), coma of the 1st degree - 4 people, coma of the 2nd–3rd degree - 1 person) and did not occur with viral neuroinfections (p 0.001). It was noted that impaired consciousness was mainly registered in young children (10 children, 91%) relative to other age groups (p 0.01), and in boys more often than in girls (p 0.05.)

Convulsive syndrome as a manifestation of neuroinfection was rare, only in 5 (8.5%) of the patients we observed with BNI. At the same time, in 60% of cases, convulsions in children developed against the background of normal body temperature as a manifestation of severe damage to the brain substance in a group of patients with meningoencephalitis and cerebral edema. However, even with the lightning-fast form of meningococcal infection, seizures can be registered in a third of sick children[5,15,17].

The structure of emergency conditions and the frequency of their occurrence in children with neuroinfections is presented in Table 3.

Table3. The structure of urgent conditions and frequency of their occurrence in children with neuroinfections

Emergency condition	Bacterial neuroinfections (n = 64)		Viral neuroinfections (n = 37)		P
	absol.	%	absol.	%	
Cerebral edema	13	20,3	2	3,1	< 0,05
Septic shock	14	22	0	0	< 0,005
Neurotoxic syndrome	2	1,7	0	0	> 0,05
Waterhouse – Friederiksen syndrome	4	5	0	0	> 0,05

As follows from Table 3, emergency conditions in children with neuroinfections directly depend on the etiology. Thus, with purulent meningitis and meningoencephalitis due to pronounced factors of pathogen aggression, swelling and swelling of the brain substance were statistically significantly more common than with viral lesions of the central nervous system (p 0.05). The clinic of edema and swelling of the brain substance was registered more often among young boys (58.3%). It is believed that brain edema develops especially rapidly and has the most severe symptoms in pneumococcal infection, which occurs in more than 50% of cases of the disease[4,11,18]. We observed children with pneumococcal lesions of the central nervous system who had a severe and prolonged course of the disease, including those caused by the clinic of edema and swelling of the brain.

The severity of BNI, especially in the case of a combination of CNS damage and septicemia, caused the course of septic shock of varying severity[16,17,19]. This condition was recorded exclusively in bacterial neuroinfections and was not found in viral lesions of the nervous system (p 0.005). Hemorrhage in the adrenal cortex (Waterhouse–Friederiksen syndrome), detected postmortally in three fatal cases with lightning-fast forms of meningococcal infection, was found only in BNI, but due to the small number of such cases, there was no statistical difference (p 0.05)[20,21].

CONCLUSION

On the territory of the Trans-Baikal Territory in the period from 2018 to 2022, bacterial neuroinfections prevailed in the structure of infectious lesions of the central nervous system with predominant registration

among boys of the first years of life. The structure of etiological causes of viral neuroinfection was dominated by enteroviruses Coxsackie and ESNO, more often registered among boys aged 4 to 15 years. The leading clinical manifestation of neuroinfections is cephalgic syndrome with hyperesthesia, as well as vomiting of central genesis and high fever. Meningeal signs do not depend on the etiology of neuroinfection, with the exception of a specific meningeal posture characteristic of bacterial lesions of the central nervous system. The longest duration of preservation of positive meningeal signs is recorded in bacterial neuroinfections. The list of urgent conditions in neuroinfections depends on the etiological cause. In bacterial lesions, the severity of the process is due to septic shock, Waterhouse –Friederiksen syndrome and the clinic of edema-swelling of the brain.

AUTHORS'S CONTRIBUTION:

Data gathering and idea owner of this study: Yerzhanova Akmaral, Kemelbekov Kanatzhan

Study design: Ayaganov Dinmukhamed, Seitkhanova Bibigul

Data gathering: Ospanova Elmira, Sarsenbayeva Gulzat

Writing and submitting manuscript: Seidakhmetova Aizat, Kylyshbekova Gulzhamal

Editing and approval of final draft: Kemelbekov Kanatzhan

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