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Incidence and Risk Factors for Seizures in Central Nervous System Infections in Childhood

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ABSTRACT

Introduction: The infections of the central nervous system remain as a public health problem in several countries and there is a direct relation between poverty and underdevelopment with high mortality and morbidity rates. Seizures represents a complication related to infections of the central nervous system, are considered a clinical emergency and requiring neurological investigation. **Objective:** In this article, we propose to describe the incidence and risk factors for seizures in central nervous system infections in childhood. **Methods:** a retrospective study was performed between October 2007 and October 2008 and all patients who were hospitalized with the diagnosis of infections of the central nervous system were analyzed. Newborns were excluded. The patients were divided into GROUP 1 (without seizures) and GROUP 2 (with seizures). **Results:** 731 patients were included, 47.75% males, with average age of 15.7 years. GROUP 1 – with fever (652/92.35%), headache (580/82.15%), vomits (550/77.9%), and viral meningitis predominance (652/93.06%). GROUP 2 – with fever (25/100%), vomits (12/48), headache (6/24%), and viral encephalitis predominance (14/56%). Ten (40%) patients from the GROUP 2 presented EEG alterations. The incidence of seizures was 3.42% and a significant statistical difference was noticed related to mean age ($p<0.000069$), presence of headache ($p<0.0000$), vomits ($p<0.0005$), stiff neck ($p<0.0105$) and drowsiness ($p<0.0265$). **Conclusions:** the occurrence of seizures during the hospitalization is significantly more frequent in cases of viral encephalitis and bacterial meningitis compared to viral meningitis. The risk of seizures increases in early ages. Headache, vomits, stiff neck and drowsiness are more frequent symptoms in children with infection of the central nervous system who presented seizures during the hospitalization.

Key works: Seizures, central nervous system infection.

RESUMO

Incidência e fatores de risco para crises epilépticas nas infecções do sistema nervoso central na infância

Introdução: a infecção do sistema nervoso central permanece como um problema de saúde pública em diversos países, havendo uma relação direta entre pobreza e subdesenvolvimento e taxas mais elevadas de morbidade e mortalidade. As crises convulsivas correspondem a uma das complicações das infecções centrais, representando uma emergência clínica e necessitando investigação neurológica. **Objetivo:** neste artigo nosso objetivo foi descrever a incidência e os fatores de risco para crises convulsivas em crianças com infecções do sistema nervoso central. **Métodos**: estudo retrospectivo realizado entre 01/10/2007 e 01/10/2008 sendo avaliados todos os pacientes internados com diagnóstico de infecção do sistema nervoso central. Foram excluídos os recém nascidos. Os pacientes foram divididos em GRUPO 1 (sem crise convulsiva) e GRUPO 2 (com crise convulsiva) para análise. **Resultados:** foram incluídos 731 paciente, 47,75% do sexo masculino, com idade média de 15,7 anos. GRUPO 1 – predomínio de febre (652/92,35%), cefaléia (580/82,15%), vômitos (550/77,90%) e do diagnóstico de meningite viral (657/93,06%). No GRUPO 2 - predomínio de febre (25/100%), vômitos (12/48%), cefaléia (6/24%) e do diagnóstico de encefalite viral (14/56%). Dez (40%) pacientes do GRUPO 2 apresentaram alteração no EEG. A incidência de crise convulsiva foi de 3,42% e houve diferença estatisticamente significativa quanto a

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idade média (p<0,000069), presença de cefaléia (*p*<0,0000), vômitos (*p*<0,0005), rigidez de nuca (*p*<0,0105) e sonolência (*p*<0,0265). **Conclusões:** crise convulsiva durante o internamento é significativamente mais freqüente nos casos de encefalite viral e meningite bacteriana quando comparado à meningite viral. Quanto menor a idade da criança maior o risco de crise convulsiva durante o internamento. Cefaléia, vômitos, rigidez de nuca e sonolência são mais freqüentes nas crianças com infecção do sistema nervoso central que apresentam crise convulsiva no internamento.

Unitermos: Crises convulsivas, infecção do sistema nervoso central.

INTRODUCTION

The infection of central nervous system (CNS) presents high prevalence in pediatric patients. The morbidity and mortality rates vary mainly according to the etiologic agent, although other factors such as age, immune condition, the early diagnosis and treatment also show great influence on prognosis.[1,2] In pre-antibiotic's epoch, infections in the CNS had high morbidity and mortality. The penicillin and sulfonamides represented a milestone in dealing with significant improvement of prognosis.[3]

The CNS infections can be classified as encephalitis and meningitis. The encephalitis is a disease characterized by inflammatory process of brain tissue due to the presence of an infectious agent, usually a virus. Meningitis is a disease characterized by inflammation of subarachnoid space and leptomeningeal membranes (pia mater and arachnoid), which may be caused by viruses, bacteria, protozoa and fungi. The etiologic agents can reach the CNS through hematogenous usually after pass over the upper airways mucous membrane, over a focus contiguous to the CNS (eg otitis, sinusitis) or direct way (eg craniocerebral trauma, neurosurgery).[4] The encephalitis and meningitis pose a public health problem in several world places, especially in the poorest countries. Not only the incidence but also the risk of neurological complications is higher in poorer countries. In Brazil, states of lower socio-economic development are those with higher rates of encephalitis/meningitis and also at greatest risk of complications.[5]

The high morbidity and mortality rates of these infections, particularly of bacterial meningitis in infants,[6] justifies the importance of clinical and laboratory aspects and the searching for factors that can predict the prognosis. The high incidence of seizures in the meningitis and encephalitis also justifies a detailed analysis of this association.

This study is aimed to identify the principal clinical and laboratory features of the CNS infections, evaluate their morbidity and mortality rates in childhood and seek factors that might help in determining the prognosis.

METHODOLOGY

It was performed a retrospective study and has been reviewed the medical charts of 731 children hospitalized at Hospital Pequeno Príncipe between 10/01/2007 and 10/01/2008. The inclusion criterion was the presence of clinical and laboratory diagnosis of CNS infection. The normal values of cerebrospinal fluid that were used for central infection diagnosis is in Table 1. After reviewing the medical records a clinical file was fulfilled containing age, gender, patient's identity number, signs and symptoms that justified the cerebrospinal fluid gather, presence of seizures and the semiology of the events. The CNS infections were classified as viral meningitis, bacterial meningitis and encephalitis in conformity to clinical data and according to the cerebrospinal fluid analysis (number of leukocytes, *erythrocyte*, glycorrhachia, *protein*, chloride, neutrophil percentage and polymorphonuclear and culture). All patients who had seizures or neurological signs were submitted to an electroencephalogram digital exam and a neuroimaging exam (CT scan or MRI). The clinical file also assessed the treatment (symptomatic, antibiotics or antiviral), the hospitalization period in infirmary and in the intensive care unit (ICU), presence of neurological sequel and use of antiepileptic drugs after discharge from hospital. All infants under 28 day-old (newborns) were excluded. There were excluded 24 medical records due to lack of data or incomplete data for analysis.

Table 1. Normal values for cerebrospinal fluid according to age

	2 months	3 months	after 3 months
Aspect	Clear	Clear	Clear
Color	Colorless	Colorless	Colorless
Leukicytes/mm³	0 - 12	0 - 4	0 - 4
Erythrocytes/mm³	Absent	Absent	Absent
Protein (mg/dl)	20 - 45	10 - 42	10 - 42
Glucose (mg/dl)	40 - 78	40 - 80	40 - 80
Cloretos	702 - 749	702 - 749	702 - 749
Gram stain	Negative	Negative	Negative

The data were tabulated in EXCEL® (Microsoft Corporations) and statistical analysis was performed using the software STATISTICA version 7. The test for difference between proportions was used for statistical analyses. Were considered statistically significant *p*-values <0.05 and highly statistically significant *p*-values <0.01.

The research project was submitted, reviewed and approved by the Research Ethics Committee in Human Beings of the Hospital Pequeno Príncipe, Curitiba, PR, Brazil, in February 2008.

RESULTS

There were included 731 patients, 349 (47.75%) males and 382 (52.26%) females, with ages ranging between 0.1- and 2,88-year-old (average of 15.7-year-old, median 4.90-year-old, standard deviation of 3.41-year-old). The patients were divided into two groups for analysis: GROUP 1 (no seizures; 706/96.58%) and GROUP 2 (with seizures, 25/3.42%).

GROUP 1: 368 (52.13%) were female and 338 (47.88%) male, with ages ranging between 0.2- and 15.7-year-old (average of 5.55-year-old, median 4.9-year-old, standard deviation of 3.34-year-old). The most frequent clinical manifestations were fever (652/92.35%), headache (580/82.15%), vomits (550/77.90%), neck stiffness (262/37.11%), irritability (61/8.64%), *drowsiness* (52/7.37%), neck pain (32/4.53%), petechiae (8/1.13%) and ataxia (7/1.00%). In this group, 657 (93.06%) patients were diagnosed with viral meningitis, 33 (4.67%) viral encephalitis and 32 (4.53%) bacterial meningitis.

GROUP 2: 14 (56%) patients were female and 11 (44%) male, with ages ranging between 0.1- and 12.9-year-old (average of 2.88 year-old, median 0.9-year-old; standard deviation of 4.25-year-old). The most frequent clinical manifestations were fever (25/100%), vomits (12/48%), headache (6/24%), *drowsiness* (6/24%), neck stiffness (3/12%) and irritability (3/12%). In this group, 14 (56%) patients were diagnosed with viral encephalitis, 7 (28%) viral meningitis and 4 (16%) bacterial meningitis. The seizures presented alternate semiology (Table 2). All patients in Group 2 were subjected to electroencephalography and imaging examinations (CT scan and/or MRI), 10 of them (40%) showed electrographic changes (Table 2) and 5 (20%) variation in neuroimaging (all suggestive of ischemic lesions).

Although no patients in this study received hospital discharge presenting neurological damage, 7 (28% of group 2) were discharged from hospital using antiepileptic drugs and also there was one decease in Group 2. The seizures incidence in children with central nervous system infection was 3.42%. The average age between the groups 1 and 2 showed high statistical significant difference ($p<0.000069$). The presence of headache ($p<0.0000$), vomits ($p<0.0005$), sniff neck ($p<0.0105$), drowsiness ($p<0.0265$) showed statistical significant difference ($p<0.000069$). Patients diagnosed with viral encephalitis ($p<0.0000$) and with diagnosis of bacterial meningitis ($p<0.0094$) had significant higher risk for seizures during the hospitalization. In Table 3 we have a statistical comparison of absolute values, percentages of the levels of significance between groups 1 and 2.

Table 2. Seizures semiology e electroencephalogram findings

	Seizure	Eletroencephalogram
1	Clonias of the R arm, lateral deviation of the eyes (R)	Slow background activity, multifocal sharp wave discharges
2	Upward deviation of the eyes, cyanosis, hypotonia	Normal
3	Tonic posture of the 4 limbs, upward deviation of the eyes	Normal
4	Clonias of the 4 limbs, fixed sight, peri-oral cyanosis, salivation	Asymmetric background activity (slower on the R)
5	Facial myoclonia, nystagmus, tonic posture of both arms	Bursts of slow waves (delta), frontal-L sharp wave discharges
6	Clonias of the 4 limbs, peri-oral cyanosis	Normal
7	Hypotonia, upward deviation of the eyes	Normal
8	Hypotonia, fixed sight, salivation	Normal
9	Clonias of the 4 limbs, tonic posture	Normal
10	Clonias of the R arm, lateral deviation of the eyes (R)	Slow background activity
11	Clonias of the 4 limbs, tonic posture	Normal
12	Tonic posture of the 4 limbs, salivation	Normal
13	Clonias of the 4 limbs, fixed sight	Normal
14	Hypotonia, upward deviation of the eyes, salivation	Normal
15	Hypotonia, fixed sight, peri-oral cyanosis	Slow background activity
16	Hypotonia e cyanosis, salivation	Asymmetric background activity (slower on the L), occipital (R), temporal (L) and frontal (L) sharp wave discharges
17	Generalized tonic-clonic seizure	Slow background activity, bilateral frontal-central sharp wave discharges
18	Generalized tonic-clonic seizure	Slow background activity, bilateral frontal sharp wave discharges
19	Tonic posture of the limbs, lateral deviation of the eyes (R)	Normal
20	Clonias of the 4 limbs, mouth deviation (L), blinking, oroalimentary automatism	Slow background activity
21	Hypotonia, upward deviation of the eyes	Normal
22	Clonias of the 4 limbs, salivation	Normal
23	Hypotonia, peri-oral cyanosis, fixed sight	Slow background activity
24	Tonic posture of the R arm, nystagmus, peri-oral cyanosis	Normal
25	Generalized hypotonia, blinking	Normal

Legend: R (right), L (left)

Table 3. Comparison of variables – absolute value, percentages and significance levels

Variables	GROUP 1 (n / %)	GROUP 2 (n / %)	*p*
female	368 / 52,13	14 / 56	0,6941
male	338 / 47,88	11 / 44	0,7028
fever	652 / 92,35	25 / 100	0,1511
headache	580 / 82,15	6 / 24	0,0000 **
vomiting	550 / 77,9	12 / 48	0,0005 **
stiff neck	262 / 37,11	3 / 12	0,0105 *
irritability	61 / 8,64	3 / 12	0,5593
drowsiness	52 / 7,37	6 / 24	0,0265 *
neck pain	32 / 4,53	0 / 0	0,2768
petechiae	8 / 1,13	0 / 0	0,5663
ataxia	7 / 1	0 / 0	0,6552
viral meningitis	657 / 93,06	7 / 28	0,0000 **
viral encephalitis	33 / 4,67	14 / 56	0,0000 **
bacterial meningitis	32 / 4,53	4 / 16	0,0094 **

* significant statistical values (p<0,05).
** very significant statistical values (p<0,01).

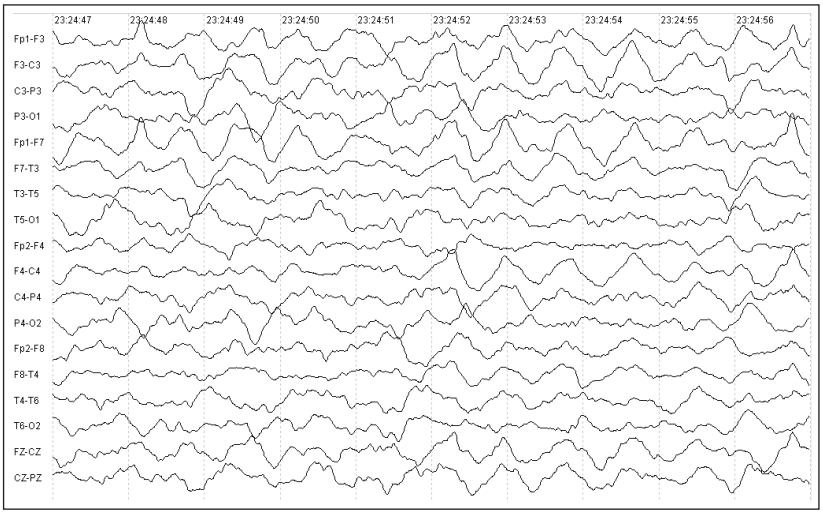

Figure 1. Electroencephalogram showing slow background activity in patient with seizure (clonias of the right arm and lateral deviation of the eyes – patient 10).

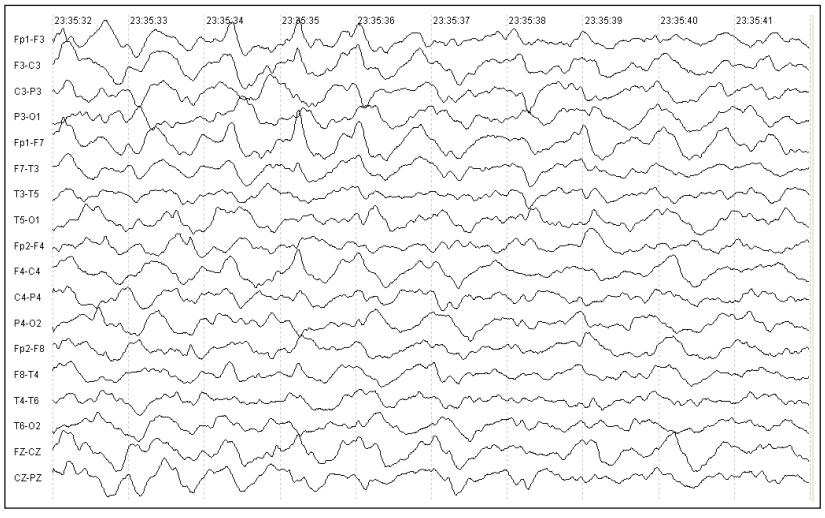

Figure 2. Electroencephalogram showing burst of slow waves in patient with seizure (facial myoclonia, nystagmus and tonic posture of both arms – patient 5).

DISCUSSION

The CNS infections are related to several complications, such as increased intracranial pressure, cerebral abscesses, ventriculitis, hydrocephalus and cranial nerves injuries. Seizures are the most frequent complication, furthermore, their presence increases the morbidity and mortality rates.[1,2]

The differentiation between the viral meningitis *symptoms*, viral encephalitis and meningitis bacteria is carried out through analysis of laboratory tests (especially the blood count, cerebrospinal fluid and blood glucose) and the clinical aspects lodged by the patient. Children with viral meningitis generally present feverish *symptoms*, cephalalgia, nausea and vomits without significant involvement of the general condition. Viral encephalitis in children usually have more acute neurological impairment, and there may be lowering of the level of consciousness (ranging from drowsiness to coma), acute ataxia, tremors, focal seizures and signs of focal neurological deficits.[7]

Lucena et al.[6] studied 116 children aged between 28-days-old and 2-years-old with bacterial meningitis and demonstrated that the most frequent signs and symptoms were fever (113/97.4%), vomits (88/75.9%), neck stiffness (84/72.4%), decreased level of consciousness (42/36.2%), seizures (40/34.5%), Brudzinski sign (34/29.3%), upper motor neuron syndrome (32/27.6%), Kernig sign (11/9.5%), alteration in cranial nerves (10/8.6%), cerebellar syndrome (9/7.8%), intracranial hypertension syndrome (5/4,3%), Lasègue sign (4/3.4%) and extrapyramidal syndrome (2/1.7%). In our study fever, cephalalgia and vomits were the most frequent signs and symptoms of central nervous system infection in groups 1 and 2.

Seizures can occur in children with CNS infection mainly due to vasculitis, thrombosis, ischemia, cerebral abscess formation and subdural collections.[8] In severe cases of central infection, where an association between vasculitis and cerebral edema occur, brain perfusion is intensively committed resulting in an increased risk of ischemic brain injury and seizures.[9] Vieira[5] evaluated 202 patients with bacterial meningitis aged between 0 and 12-year-old showing that 41.1% had neurological complications, and the most common problems were seizures, occurring in 38 patients (18.8%).

In a recent study published, Davenport et al.[10] evaluated 81 children with bacterial meningitis with an average age of 7.5-year-old and showed that 18.5% evolved with neurological complications, the most frequent were seizures (8/9.9%), cerebral ischemia (5/6.2%), hydrocephalus (4/4.9%) and syndrome of inappropriate secretion of antidiuretic hormone (3/3.7%). The average values of cellularity, cerebrospinal fluid (CSF) glucose concentrations, *proteinorachia*, positive culture in blood and cerebrospinal fluid were also evaluated and the authors concluded that the three major risk factors for neurological complications were the positive blood culture, high proteinorachia value and low age. The neurological sequelae related to bacterial meningitis are strongly dependent of the child's age. According to Bresolin,[11] the most common injuries in children younger than 2 months old are delayed neuropsychomotor development, hydrocephalus and seizures, while in children over 18 months seizures and deafness are the most frequent complications.

In our study, the seizures incidence (25/3.42%) was lower than reported in the international literature. The results obtained in our study, as demonstrated in the literature, showed that there is an inverse correlation between age and seizures risk in children with central nervous system infection and also that both viral encephalitis and bacterial meningitis have a significant higher risk of seizure compared to cases of viral meningitis.

Analyzing the signs and symptoms that the patients showed in hospital admission moment we verified that cephalalgia, vomiting, neck stiffness and drowsiness were significantly more frequent in children who subsequently develop seizures during the hospitalization. Moreover, fever, irritability, neck pain, petechiae and ataxia were not more frequent in children with central nervous system infection who developed seizures. We also evidenced that *EEG* is a medical exam that demonstrates a sensitivity of 40% for abnormality and should be performed in all children with central nervous system infection who present seizures during the hospitalization.

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