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ISSUES CONCERNING ACUTE ENCEPHALITIS DURING SEASONS OF FLU EPIDEMICS

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During the seasons of flu epidemics in the last five years (winter months, 1997-2002), 49 patients who meet criteria for influenza associated encephalitis/encephalopathy (IAEE) with versatile clinical picture and expression of the illness, have been treated. Especially neurovirulent was last influenza epidemic (december/2001-martch/2002), when 16 such patients were registered. Initial CSF finding in all 16 treated patients showed low or normal CSF WBC count, with increased or normal proteinorachy, finding, consistent with IAEE clinical syndrome in the course of influenza infection, characterized with high fever, acute beginning of brain dysfunction, convulsions, and lost of consciousness, but at the same time with (encephalitis), or, with no (encephalopathy) inflammatory changes in the CSF. Influenza viral infection was confirmed serologically (IIF and ELISA-IgM) in all patients, and, in two of them, with isolation of influenza virus from nasalpharyngeal swabs (A/H3N2, sub-typed as Panama/2007/99). In all patients fever and symptoms of upper respiratory tract infection proceeded neurological complications, and had rapid beginning and development. All patients were with altered level of consciousness, 9 of them developed generalized tonic-clonic convulsions; in three patients focal neurological symptoms with hemiparesis were registered. Despite intensive treatment and care, six patients died, three had residual neurologic seguelae, and the other seven recovered completely. IAEE patients with coagulopathy and hepatic dysfunction tended to have a poor prognosis. All six deceased patients had hepatic dysfunction and four of them blood coagulation system abnormalities associated with bleeding diathesis. Serum levels of ALT/AST and LDH were more elevated in the deceased patients than in patients with sequelae and a full recovery.

One of the most common causes for infections during winter months worldwide is influenza viral infection. Variety of different form of CNS involvement can be detected during influenza seasons. Influenza A virus occasionally causes acute encephalopathy and postinfection encephalitis. Influenza encephalopathy occurs in the acute phase of influenza syndrome, and it is extremely rare for the viruses to be isolated from the CSF of an adult. Recently, there are published reports in different influential journals, describing patients with acute encephalitis or encephalopathy presented with fever (high temperature), disturbed state of consciousness and recurrent convulsions in children (although recently found with increased occurance in adults) during influenza epidemics. This is first reported in Japan, but such conditions now also occur in other parts of world. Epidemics caused by influenza A virus are reported as extremely neurovirulent during the 1997-2001 in Japan, associated with high mortality in patients with influenza associated encephalitis/encephalopaty. There is some kind of consensus made about definition of acute encephalopathy, that is mentioned in the literature, and is described as clinical syndrome characterized with acute beginning of brain dysfunction, convulsions, and lost of consciousness, but at the same time with no inflammatory changes in the cerebrospinal fluid, such is CSF WBC count, whereas, in their presence we use the term encephalitis. Probability for such an conditions is particularly high during the seasons of flu epidemics. Influenza virus is a leading cause among the infectious agents to which acute necrotizing encephalopathy has been ascribed. Normal CSF

findings are not rare in patients with influenza associated encephalitis/encephalopathy, and in some cases there are not found even inflammatory changes (reactions) in brain tissue examined post mortem. It is estimated that an average of 100 children a year dies from influenza associated encephalitis/encephalopathy in Japan. Although some autorities suggest that administration of antipyretics and insufficient vaccination against influenza are major cause for progression of influenza infection to encephalitis/encephalopathy, true cause for this conditions remain obscure.

Main purpose of this study was to determine presence and plentitude of patients who meet above mentioned criteria for influenza associated encephalitis/encepahlopathy during the seasons of flu epidemics in R.Macedonia, and to make an effort, over our own analysis, to explain possible pathogenesis of this serious, lifetreatening complication of influenza viral infection. Clinic for infectious diseases in Skopje is central institution and the only one which offers tertian health care in our country, and majority of patients with influenza associated encephalitis/encephalopathy are committed in our hospital, and accordingly the number of hospitalized patients is in high correlation with the actual incidence of the same in the country.

MATERIAL AND METHODS

In the last five years (december/1997-martch/2002) during winter months, that is during the seasons of flu epidemics, there have been 49 treated (annual average 9.8) patients who meet the above mentioned criteria for influenza associated encephalitis/encephalopathy with versatile clinical picture and expression of the illness. Despite intensive treatment and care, full recovery has been succeeded only in 19 (38.8%) patients, 20 (40.8%) patients died, and permanent neurological sequels were found in 10 (20.4%) patients - four with hemiparesis, 6 with epilepsy, and 4 with mental retardation. Especially neurovirulent was last influenza epidemic (december/2001-martch/2002), when 16 patients with influenza associated encephalitis/encephaopathy were registered, which compared to the mean annually treated patients represents dramatically increase of 93.9%. Influenza viral infection was confirmed serologically in all patients (test of indirect immune fluorescence-IIF and ELISA-technique /ELISA-IgM), while in two of them, in addition, we isolated influenza virus from nasal-pharyngeal swabs (A/H3N2, sub-typed as Panama/2007/99). We analyzed clinical symptoms, clinical picture and some laboratory and biochemical parameters (including cytokines in 5 patients), electrophysiological and neuroradiological findings in all patients with influenza associated encephalitis/encephalopathy treated during the last flu epidemic. During hospitalization, in several ocasions computer tomography (CTM), nuclear magnetic resonance (MRI) and electroencephalography have been made.

RESULTS

CLINICAL CHARACTERISTICS, NEURORADIOLOGICAL FINDINGS AND TREATMENT

Average age of all treated patients was 36 year (from 5-76 years), seven male, and nine female. None of these patients was previously immunized with influenza vaccine. There was no data found in familial anamnesis and or history of previous diseases, which could offer connection with development of these complications. All patients, except three, had normal psychomotor development. In relation to administration of antipyretic agents, three patients were treated with aspirin before developing complications. In all patients fever and symptoms of upper respiratory tract infection proceeded neurological complications, and had rapid beginning and development. Initial pyrexia was from 38.0(C to 40.4(C (average of 39.2(C). All patients were with altered level of consciousness, and 9 of them developed generalized tonic-clonic convulsions that lasted from several minutes to few hours during first several days of elevated temperature. In three patients focal neurological symptoms with hemiparesis were registered. Electroencephalography was done on 13 patients, and in 8 there was high voltage slow wave activity, three had periodical lateral epileptic discharge, one with focal spikes, and almost normal brain activity was found in one patient. Neuro radiological findings (CTM and MRI) were divided into three categories: 1-difuse brain edema; 2-

simetrical involvement of thalamus, brain stem and cerebellum, e.g. acute necrotizing encephalitis and 3-normal findings. Despite intensive treatment, 6 patients died, permanent neurological sequels were registered in three, and complete recovery had 7 patients.

LABORATORY FINDINGS

Initial CSF finding in all treated patients showed low or normal CSF WBC count, with increased or normal proteinorachy. Laboratory and biochemical findings were summarized and divided into three groups according illness output: deceased, recovered with sequels, and completely recovered. All 6 deceased patients had obvious hepatic dysfunction and disseminated intravascular coagulation (DIC). Serum levels of ALT/AST and LDH were elevated in higher level in deceased patients (ALT/ASTn=6, 145/128 IU/L; rang 58/49-296/304 IU/L and LDHn=4, 988 IU/L; rang 684-1655 IU/L) in relation to recovered patients with sequels (ALT/ASTn=3, 108/98 IU/L, rang 54/50-173/154 IU/L; and LDHn=3, 667 IU/L, rang 466-920 IU/L) and completely cured patients (ALT/ASTn=7, 64/68 IU/L; rang 28/30-94/88 IU/L; and LDHn=4, 524 IU/L; rang 482-684 IU/L). Disorders of blood coagulation associated with hemorrhagic diathesis were registered in 4 patients and all of them died. Generally speaking, patients with coagulopathy and hepatic dysfunction had poor prognosis. In addition, two patients had hypoglycemia (one died), and two other, had increased level of azotemia. Plasma cytokine concentrations (Il-6 and TNF-() were determined in 5 patients hospitalized at the Clinic less than 24 h after onset of symptoms of the disease. In two patients with fatal outcome cytokine concentrations were extremely increased, and one, also with fatal outcome, had normal plasma cytokine concentration. It is important to mention that plasma cytokine concentrations were very variable, and one patient who recovered with sequels had also somewhat increased level of them. The duration of the illness prior to hospitalization was also variable, so it was difficult to make proper statistic analysis and to determine the correlation of illness prognosis and outcome according to plasma cytokine concentrations.

DISCUSSION AND CONCLUSIONS

There are more and more reports describing severe forms of acute encephalitis/encephalopathy during seasons of influenza epidemics, and most of them come from Japan, and generally describes cases of pediatric population. Most isolates are influenza A virus, mostly H3N2, and rarely H1N1. It has been shown that this complication happens in people who were not immunized with influenza vaccine, and risk factor for poor outcome is thrombocyte depletion and increase of serum concentrations of aminotransferases (glutamat oxalacetic transaminase). Pathogenesis of influenza associated encephalitis/encephalopathy still remains uncertain. Although there are reports with positive findings of viral antigen in Pyrkiniev's cells in cerebellum in different pontal neurons, discovered in brain material on autopsy, for now prevails the opinion that direct brain invasion with influenza viruses is not very common, and that it occurs only in cases which manifest with progressive and severe clinical picture, with brain edema and fatal outcome and is attributed to cytokines. Although variable, serum levels of Il-6 are highest in our patients with the most severe prognosis, as well. Other researches also associate high plasmatic cytokine concentration with progression toward encephalitis/encephalopathy. Fast production of several proinflammatory cytokines could initiate disruption of blood-brain barrier thus inducing severe brain edema, as well as hepatic dysfunction, multiorgan failure and disseminated intravascular coagulation. These changes as result of hypercytokinemia could represent major pathological characteristic of the illness. It is considered that diffuse brain edema and symmetrical lesions in thalamus are result of hyper permeable vascular lesions caused by cytokines. Besides hypercytokinemia, we should look for other reasons like apoptosis; delayed neuron death or secondary cell death as results of prolonged convulsions or hypoxia and in some forms secondary encephalitis can not be excluded. The conclusion is that influenza associated encephalitis/encephalopathy expresses versatile clinical finding, that pathogenesis is very variable, and additional analysis is necessary. Hypercytokinemia is only one of many possible explanations for the development and poor outcome of the disease.

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