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Early Identification of Influenza Related Acute Necrotizing Encephalopathy by Clinical Manifestations and Laboratory Index

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Abstract

Background: To explore the early clinical features and laboratory findings of influenza-associated acute necrotizing encephalopathy (IANE). ***Methods***: The demographics data, clinical manifestations, and laboratory indicators of cases diagnosed with IANE and influenza with febrile convulsions (FS), respectively, admitted to Guangzhou Women and Children's Medical Center from January 2016 to January 2020 were retrospectively analyzed. ***Results***: Among the 25 cases of IANE, there were 9 males and 16 females, aged 3 to 6 years. The mortality rate was 40.00% (10/25). Influenza virus type A in 9 cases (36.00%) and influenza virus type B in 10 cases (40.00%). The main clinical manifestations of children with IANE were acute disorders of consciousness (64.00%, 16/25) and convulsions (72.00%, 18/25), which were statistically significant when compared with the FS group ($P < 0.05$). Typical changes on cranial MRI of IANE were cerebral edema, typically with symmetric necrosis of the thalamus and other brain structures. Significant differences ($P < 0.05$) existed between the IANE and FS groups in laboratory indicators for ALT, AST, CK-MB, LDH, cerebrospinal fluid (CSF) microprotein, CSF LDH, which were above the normal reference range. In addition, logistic regression analysis showed that LDH ≥ 348.5 U/L predicted a significantly higher risk of IANE. ***Conclusions***: Children with influenza present early with acute impairment of consciousness or convulsive seizures, or with elevated AST, ALT, CK-MB, LDH, and CSF protein and CSF LDH, especially if blood LDH is ≥348.5 U/L, should be closely evaluated and alerted to the possibility of IANE.

Keywords

Children, Influenza, Encephalopathy, Clinical Characteristics, Laboratory Index

1. Introduction

Influenza is a highly contagious respiratory transmitted disease with a high prevalence in winter and spring. Influenza in children is a major cause of morbidity and mortality worldwide, with higher incidence rates each year. Influenza viruses, belonging to the family Orthomyxoviridae, primarily affect the respiratory system. And influenza A and B viruses are the main prevalent viruses of influenza. The typical clinical manifestations of influenza-infected persons are acute fever, muscle pain, headache, accompanied by respiratory symptoms. Some patients may not have any typical clinical features. Symptoms in young children are even characterized by high fever, and gastrointestinal complaints such as nausea, vomiting, diarrhea, and loss of appetite.

Influenza viruses usually invade the respiratory tract, but can also affect other systems such as digestive, nervous, cardiovascular and so on. Although the infection is usually self-limiting, children have a higher risk of complications when involving the neurological and cardiovascular systems, causing complications such as IANE, multiple organ dysfunction syndrome, and septic shock, leading to death in children [1] [2]. There are various neurological complications of influenza, including febrile convulsion, encephalopathy, encephalitis, aseptic meningitis, acute cerebellar ataxia, myelitis, Guillain Barre syndrome, acute disseminated encephalomyelitis (ADEM), occasional cerebrovascular diseases and so on, some of which can be life-threatening or leave severe neurological sequelae. Neurological complication, often defined as IANE, is rare but is an important complication of influenza infection with approximate three-quarters of cases regarding children and leading up to 30% of mortality in children [3] [4]. The current lack of characteristic clinical manifestations or effective biomarkers of IANE and the exact pathogenesis and risk factors are not clear, have made early diagnosis relatively difficult [5] [6] [7]. In this study, we review and compare the demographic data, clinical manifestations, and laboratory findings of a total of 25 cases hospitalized with a diagnosis of IANE and 57 cases diagnosed with FS from January 2016 to January 2020 in Guangzhou Women's and Children's Medical Center, aiming to explore the characteristic clinical manifestations and available biomarkers of IANE.

2. Methods

2.1. Patients

This study included 25 patients with IANE and 57 patients with FS who were admitted to Guangzhou Women and Children's Medical Center between Janu-

ary 2016 and January 2020. The ethics committee approved this study of Guangzhou Women and Children's Medical Center, Guangzhou Medical University.

2.1.1. Inclusion Criteria

1) age < 18 years of age; 2) positive real-time PCR detection of influenza virus in nasal and pharyngeal swabs; 3) presence of symptoms and signs of nervous system injury, such as seizures, rapid cognitive impairment, mental changes, loss of consciousness, or coma.

(A) IANE definition [7] [8]

1) age < 18 years; 2) respiratory specimen positive for influenza virus; 3) the emergence or development of a neurological symptom in influenza infection, such as convulsion, alteration of consciousness, rapidly progressive coma; 4) CSF white blood cell count is normal, and protein is normal or elevated; 5) the abnormal neuroradiological finding in Neuroimaging, including edema, hemorrhage, and bilateral thalamic lesions; 6) exclusion of brain dysfunction caused by other diseases.

(B) FS definition [9]

1) age < 18 years; 2) respiratory specimen positive for influenza virus; 3) convulsions with fever, consciousness after convulsions, and no more than 2 convulsive episodes during the course of the disease; 4) no abnormalities in cerebrospinal fluid examination and cranial imaging.

2.1.2. Exclusion Criteria

1) admission > 3 days after onset; 2) absence of >30% of clinical data; 3) co-infection with other pathogens such as enterovirus, herpes simplex virus, cytomegalovirus, mycoplasma, or bacteria; 4) presence of coexisting conditions such as traumatic brain injury, sequelae of viral encephalitis, epilepsy, psychomotor retardation, or metabolic diseases; 5) neurological complications other than FS and IANE, such as Influenza-Associated Encephalopathy, Influenza-Associated Acute Encephalitis, or Post-Influenza Encephalitis.

2.2. Data Collection

We take the retrospective method in this study. Data on demographics, clinical presentation, laboratory findings, and neuroimaging findings were collected. Demographic data included age, gender, virus type. Clinical data included neurological symptoms (convulsion, alteration of consciousness, rapidly progressive coma). Results of routine blood test, the comprehensive metabolic panel (including alanine transaminase (ALT), aspartate transaminase (AST), creatine kinase (CK), lactate dehydrogenase (LDH), hypersensitive C-reactive protein (CRP), and lactate), routine and biochemical test in CSF, and pathogenetic test in blood/nasal swabs/CSF were collected in Laboratory and microbiologic data. And routine blood test, the comprehensive metabolic panel, and pathogenetic test in blood/nasal swabs are usually taken on day 1 when patients admitted to the hospital. And neuroimaging data included CT and MRI, diagnosed by a senior pe-

diatric radiologist (more than ten years experiences). The reference range of laboratory findings is based on the relevant data from Guangzhou Women and Children Medical Center.

2.3. Data Analyses

All statistical analyses were performed using the SPSS 26.0 software. Categorical data were presented as frequency with the corresponding percentage. The Chi-squared or Fisher exact test was used to compare categorical variables. Continuous data were tested for normality using the Shapiro-Wilk method. Continuous data that did not conform to normal distribution were expressed as median with the interquartile range (IQR), and compared between groups by non-parametric test. The measurement data conforming to normal distribution were expressed as mean ± standard deviation (Mean ± SD), and t-test was used for comparison between groups. ROC curve analysis was used to calculate the area under the curve and determine the optimal critical value, and the indicators with significant differences in the univariate analysis were then subjected to dichotomous logistic regression analysis. Two-tailed P-values of <0.05 were considered statistically significant.

3. Results

3.1. Demographics and Clinical Characteristics

A total of 312 children were hospitalized with influenza and neurological symptoms from January 2016 to January 2020. Among them, a total of 25 children with IANE and 57 children with FS were finally included in this study (Figure 1), and their demographics data and clinical manifestations were presented in Table 1. Statistical differences were found between the two groups of children in gender, age, mortality, influenza virus type, impairment of consciousness, and a

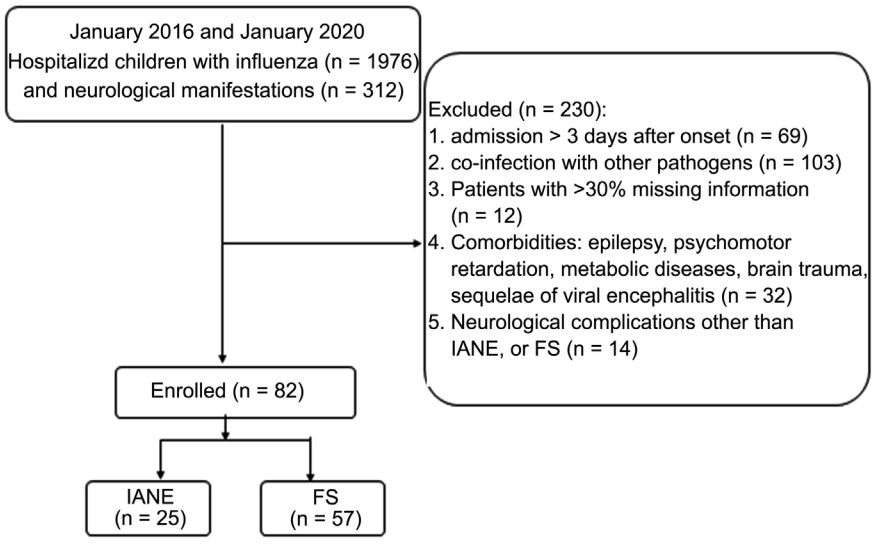

Figure 1. Procedures for inclusion and exclusion of IANE and FS.

Table 1. Demographics and clinical characteristics of the children with IANE and FS.

Variable	IANE, n = 25	FS, n = 57	U/x^2	P
Male (%)	9 (36.00)	38 (66.67)	6.68	0.01
Age (months)	52.20 (39.01, 80.46)	37.57 (25.55, 61.18)	496	0.029
Month of onset			8.243	0.156
December to February	11 (44.00)	32 (56.14)		
March to May	10 (40.00)	20 (35.09)		
June to August	4 (16.00)	4 (7.02)		
September to November	0 (0.00)	1 (1.75)		
Death (%)	10 (40.00)	0 (0.00)	22.365	<0.001
Influenza virus type			13.387	0.001
FA (%)	9 (36.00)	43 (75.44)		
H1N1 (%)	6 (24.00)	2 (3.51)		
FB (%)	10 (40.00)	12 (21.05)		
Onset (days)	2 (1,3)	2 (2,3)	585.5	0.172
Fever > 39˚C	19 (76.00)	28 (49.12)	17.465	0.0475
Vomiting	7 (28.00)	10 (17.54)	9.185	0.105
Headache	4 (16.00)	17 (29.82)	13.365	0.0772
Neurological symptoms				
Impairment of consciousness (%)	16 (64.00)	2 (3.51)	38.977	<0.001
Convulsive episodes			32.397	<0.001
0 (%)	7 (28.00)	0 (0)		
1 - 2 (%)	12 (48.00)	57 (100.00)		
≥3 (%)	6 (24.00)	0 (0)		

number of convulsive episodes between the two groups (P < 0.05). In the IANE group, 36.00% (9/25) of the children were male, the age of onset was 4.35 (3.25 - 6.71) years, and the mortality rate was 40.00% (10/25). In contrast, 66.67% (38/57) of the children in the FS group were male, with an age of onset of 3.13 (2.13 - 5.10) years, and none of the children died. In the IANE group, the proportions of FA, FB, and HINI were 36.00% (9/25), 40.00% (10/25), and 24.00% (6/25). Respectively, FA accounted for 75.44% (43/57) of the FS group. The main clinical manifestations in the IANE group were acute impairment of consciousness (64.00%, 16/25) and In the IANE group, 33.33% (6/18) of the children had more than two convulsions, while no child in the FS group had more than two convulsions (0.00%, 0/57) and few changes in consciousness (3.51%, 2/57). There was no significant difference between them within three days of onset (P = 0.172).

3.2. Laboratory Findings

Laboratory tests in the IANE and FS groups are shown in Table 2 and Table 3. significant differences ($P < 0.05$) existed between the IANE and FS groups in ALT, AST, γ-GT, ALP, ALB, CK-MB, LDH, DBIL, creatinine, hypersensitive CRP, PCT, and platelets. In addition, ALT, AST, LDH, and CK-MB in the IANE group were above the normal reference range, while these indicators were within the normal reference range in the FS group. Although the mean platelet count in the IANE group was in the reference range, the mean platelet count in their ten deaths was $124.9 \pm 98.81 * 10^9$/L, which was below the reference range. CSF protein and CSF LDH in the IANE group were significantly higher than in the FS group ($P < 0.05$), while CSF leukocyte count and CSF glucose levels were in the IANE and FS groups were within the normal reference range. There was no significant difference between the two groups ($P > 0.05$).

Table 2. Laboratory findings of the children with IANE and FS.

Variable	Normal reference range	IANE, n = 25	FS, n = 57	U/t	P
Comprehensive metabolic panel					
ALT (U/L)	9 - 50	162.00 (37.00, 906.50)	16.00 (12.15, 21.75)	175.5000	<0.001
AST (U/L)	5 - 60	251.00 (92.00, 780.00)	39.00 (32.25, 45.75)	104.000	<0.001
γ-GT (U/L)	10 - 60	19.00 (11.50, 38.55)	11.00 (9.00, 12.00)	305.000	0.010
ALP (U/L)	118 - 390	177.44 ± 82.04	237.70 ± 50.79	3.393	0.002
Amylase (U/L)	35 - 135	75.00 (47.00, 186.00)	62.50 (46.50, 76.25)	510.500	0.053
LDH (U/L)	159 - 322	705.00 (461.50, 2323.50)	278.50 (238.50, 317.75)	93.500	<0.001
CK (U/L)	45 - 390	387.00 (169.50, 852.00)	150.00 (95.50, 250.75)	369.500	0.001
CK-MB (U/L)	0 - 37	62.00 (36.00, 113.50)	22.00 (18.00, 30.75)	173.000	<0.001
Albumin (g/L)	40 - 55	38.83 ± 6.85	42.82 ± 2.91	2.802	0.009
UA (μmol/L)	90 - 420	407.00 (235.00, 517.50)	288.00 (245.50, 323.50)	538.500	0.099
IBIL (μmol/L)	2 - 13.7	3.40 (1.70, 7.50)	2.65 (1.90, 3.78)	607.500	0.344
DBIL (μmol/L)	0 - 7	2.30 (1.60, 5.75)	1.50 (1.20, 1.90)	352.500	<0.001
Lipase (U/L)	13 - 60	45.00 (28.00, 131.55)	39.55 (32.00, 44.80)	562.500	0.160
Cr (μmol/L)	18 - 62	37.00 (28.50, 55.00)	27.00 (23.25, 32.50)	379.500	0.001
TBIL (μmol/L)	2 - 17	5.60 (3.40, 12.65)	4.40 (3.33, 6.43)	573.500	0.196
Hypersensitive CRP (mg/L)	0 - 6	11.12 (4.25, 25.42)	4.58 (2.30, 13.34)	456.000	0.013
PCT (ng/ml)	< 0.1	1.14 (0.44, 11.00)	0.24 (0.13, 0.72)	303.500	0.009
Routine blood test					
Leukocyte ($\times 10^9$/L)	5 - 12	7.54 ± 4.15	7.89 ± 3.07	0.178	0.859
hemoglobin (g/L)	105 - 145	109.00 (95.25, 130.25)	119.00 (113.25, 124.00)	593.500	0.230
Neutrophil ratio (%)	40 - 60	70.70 (62.35, 85.13)	70.65 (49.48, 82.18)	544.500	0.091
Platelet ($\times 10^9$/L)	125 - 350	193.56 ± 97.21	233.64 ± 60.08	2.969	0.005

3.3. Neuroimaging Findings

A total of 37 children in the FS group underwent cranial CT or MRI examinations, and none showed abnormal changes. In contrast, 88.89% (16/18) of children in the IANE group showed abnormal changes in cranial CT or MRI examinations, mainly characterized by cerebral edema, typically symmetric necrosis of the thalamus or other brain structures, especially in the brainstem, periaqueductal white matter, and cerebellar medulla. Figure 2 shows the typical cranial MRI presentation of a child in the IANE group.

3.4. ROC Curve Analysis

The results of ROC curve analysis of laboratory indicators that were statistically different between the two groups are shown in Figure 3 and Table 4 and Table 5. Among them, AST, LDH, CSF protein, and CSF LDH had good diagnostic efficacy, but the specificity of all these indicators was low. Comparing with other indices, blood LDH had the highest sensitivity and the comprehensive correlation of sensitivity and specificity was better.

3.5. Binary Logistic Regression Analysis

The indicators with significant differences in the univariate analysis, including AST, LDH, CSF protein, CSF LDH, impairment of consciousness, and the number of convulsions, were included in the logistic regression analysis, and the results are shown in Table 6. Of which only LDH was significant in the regression equation, and the risk of IANE was significantly higher when LDH ≥ 348.5 U/L.

Table 3. Cerebrospinal fluid results of the children with IANE and FS.

Variable	Normal reference range	IANE, n = 22	FS, n = 20	U	P
CSF Leukocyte ($\times 10^6$/L)	0 - 15	4.00 (1.00, 6.25)	2.00 (1.00, 3.75)	148.000	0.065
CSF protein (g/L)	0.15 - 0.45	0.85 (0.27, 1.73)	0.22 (0.17, 0.25)	59.000	<0.001
CSF glucose levels (mmol/L)	2.8 - 4.2	3.58 (3.18, 4, 48)	3.54 (3.17, 3.66)	198.500	0.588
CSF LDH (U/L)	8 - 50	59.00 (25.00, 155.75)	18.00 (15.00, 25.75)	50.000	<0.001
CSF hypersensitive CRP (mg/L)	0 - 0.01	0.30 (0.09, 0.47)	0.30 (0.30, 0.30)	261.500	0.920

Table 4. ROC curve analysis of each index.

Variable	Area under curve	Standard error	Asymptotic significance	95% CI	
				lower limit	upper limit
ALT (U/L)	0.833	0.066	0.000	0.703	0.963
AST (U/L)	0.884	0.056	0.000	0.774	0.994
LDH (U/L)	0.925	0.047	0.000	0.833	1.000
CK-MB (U/L)	0.828	0.072	0.000	0.688	0.969
DBIL (μmol/L)	0.763	0.080	0.004	0.606	0.919
CSF protein (g/L)	0.866	0.059	0.000	0.750	0.982
CSF LDH (U/L)	0.886	0.049	0.000	0.791	0.982

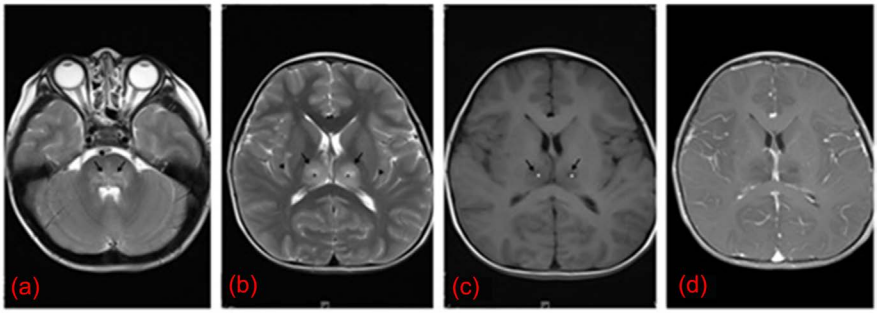

Figure 2. Cranial MRI of a patient with IANE (from left to right): (a) focal slightly elevated signal of the dorsal brainstem in T2WI (arrow); (b) mildly elevated symmetric signal of the bilateral thalamus in T2WI (arrow), with even higher capsule-like signal intensity in center (*); (c) mildly reduced the bilateral thalamus symmetric signal (arrow)in T1WI with even lower central saccade signal intensity (*); (d) no significant signal elevation of the bilateral thalamic lesions in T1WI enhancement scan.

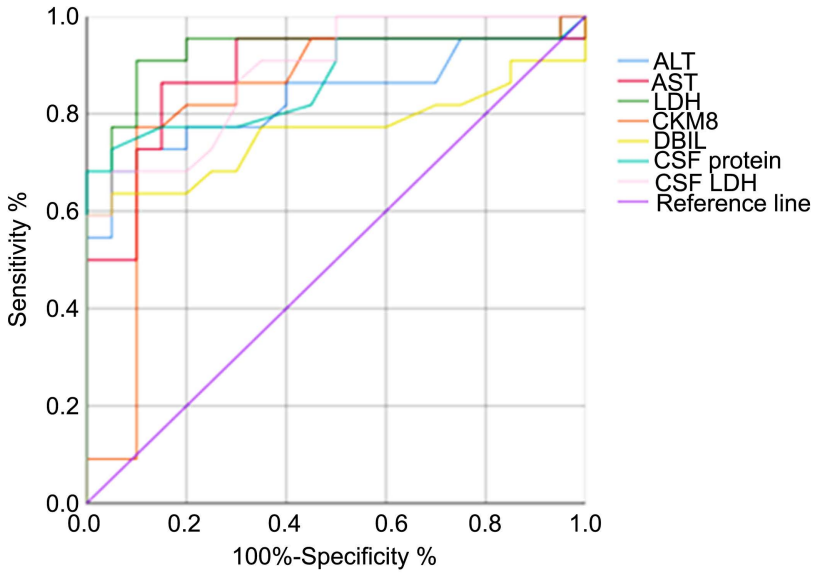

Figure 3. ROC curve of IANE predicted by each index.

Table 5. Effectiveness of various indicators in predicting IANE.

Variable	Optimum critical value	Sensitivity (%)	Specificity (%)	Youden index
AST (U/L)	72	0.864	0.15	0.714
LDH (U/L)	348.5	0.909	0.1	0.809
CSF protein (g/L)	0.39	0.682	0.0	0.682
CSF LDH (U/L)	31.5	0.682	0.05	0.632

Table 6. Multivariate analysis of IANE prediction.

Variable	B value	Standard error	Wald	Degree of freedom	Significance	Exp (B)	95% CI	
							lower limit	upper limit
LDH (U/L)	3.114	1.121	7.721	1	0.005	22.500	2.503	202.287

4. Discussion

Influenza is a common infectious disease worldwide. While mainly invading the respiratory tract, influenza viruses can cause neurological damage in some cases, leading to a series of neurological syndromes. The morbidity and mortality rates of neurological damages due to influenza are high, especially in children [4] [10]. Among them, IANE can progress rapidly and even cause death or leave permanent neurological sequelae in the short term [11]. The mortality rate of IANE in this study was as high as 40%. However, there is still a lack of specific clinical manifestations and laboratory indices for the diagnosis of IANE, and there are relatively few reports on it [5] [6] [7]. The diagnostic criteria of IANE suggested by Mizuguchi *et al.* [8] are now used as the main reference standard, among which cranial imaging is vitally important in the diagnosis and assessment of prognosis. However, cranial imaging has not been effectively performed in all children due to various factors such as medical condition, medical conditions and patients' wishes. Therefore, we need some simple and easy predictors with rapid results to enable early and rapid identification of IANE.

In this study, there was no significant difference in the prevalence between males and females in the IANE group, with ages ranging from 8 months to 11 years and a mean age of 4.4 years, which is consistent with the literature reporting that IANE occurs from 24 d - 13 years of age and is more common in children under 5 years of age [5] [10] [12]. Surana P *et al.* [13] reported that influenza-associated encephalopathy (IAE) and IANE are caused primarily by influenza virus type A, of which H1N1 was the most common. In contrast, FA and FB accounted for 36.00% and 40.00% of IANE cases in this study, with no significant difference between them, suggesting that although FB causes relatively minor neurological damage, it can also lead to severe cases and even cause death. The clinical presentation of IANE lacks specificity and is reported in the literature [5] [7] [14] to be characterized by rapid progression to encephalopathy, coma, or death within 1 - 2 days after the onset of the disease. In this study, the main clinical manifestations of children in the IANE group were acute impairment of consciousness (64.00%, 16/25) and convulsions (72.00%, 18/25), of which 33.33% (6/18) could have more than two convulsions. In contrast, no child in the FS group had more than two convulsions (0.00%, 0/57), while alterations in consciousness were rarely seen (3.51%, 2/57). In addition, children in both the IANE and FS groups developed neurological symptoms within 2 - 3 days of the onset of the disease, which is consistent with literature reports. This suggests that children with influenza need to be on high alert for IANE when they present with frequent convulsions and rapid consciousness impairment at an early stage.

IANE patients lack specific laboratory indicators, but some studies have reported that most IANE patients have significant changes in biochemical indicators within about 48 hours of admission [6]. In this study, we found that children in the IANE group showed changes in ALT, AST, CK, PCT, LDH, and PLT after admission, which were similar to the results of the above study. Consistent

with the results reported in previous literature [6] [8] [14] [15], ALT, AST, CK, blood LDH and CSF LDH and CSF protein levels were significantly higher in children in the IANE group compared with the FS group in this study. Some studies [16] [17] [18] reported that the mechanisms of neurological injury in influenza include endothelial damage. In this study, platelets were found to be below the reference range in all cases of IANE deaths, suggesting a high possibility of concomitant neurological symptoms and poor prognosis in children with influenza with reduced platelets. In addition, logistic regression analysis showed that LDH ≥ 348.5 U/L predicted a significantly higher risk of IANE, suggesting that elevated LDH could be an important reference for the diagnosis of IANE. Consistent with previous reports [19] [20], the results of this study showed that the early appearance of elevated AST, LDH, CK, and reduced platelets were associated with the development of IANE and poor prognosis, so influenza patients with neurological symptoms followed by abnormalities in the above indicators need to be highly alert for the development of IANE.

In summary, in children under 5 years of age admitted to the hospital with neurological symptoms of influenza, if they present early with acute impairment of consciousness, with or without convulsive seizures, and the first biochemical indexes AST, LDH, and CSF protein and CSF lactate dehydrogenase are elevated and platelets are decreased within 48 h after admission, especially when blood LDH ≥ 348.5 U/L, they need to be closely evaluated and alerted to the ANE, the possibility of occurrence, improve neurological related examinations as soon as possible, and give relevant interventions as early as possible to reduce the occurrence of death and sequelae. This study was conducted in only one hospital, with limited sample size and limitations, and the ability of early identification of IANE needs to be improved. Future larger studies and further validation and analysis of these biochemical indicators in future clinical cases may be needed.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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