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ORIGINAL PAPER

Encephalitis, meningitis, and acute cerebellar ataxia as neurological complications of VZV infection in children. A retrospective study

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ABSTRACT

Aim of the study: Varicella is a disease with potentially severe complications. The objective of this study was to assess the specific clinical picture of neurological complications of VZV in the form of encephalitis, meningitis, and acute cerebellar ataxia among hospitalised children.

Material and methods: The study was designed as a retrospective analysis, based on reviewing the medical records and collecting post-hospitalisation questionnaires of children admitted to the hospital for varicella complications between January 2009 and December 2018. None of the patients was vaccinated. Patients were divided into groups based on the type of neurological diagnosis. We analysed the results of the additional tests performed, their significance for the final diagnosis, and predictive validity. Statistical analysis of data was performed, and the results were compared with available data.

Results: A link between age and type of neurological complication was found. Diversity in the length of hospitalisation as well as in the number of additional tests necessary for a final diagnosis was established. None of the analysed clinical parameters and additional tests was found to be a potential predictor linked with the possibility of sequels in our study. Children with encephalitis had a significantly higher risk of neurological sequelae at the moment of discharge.

Conclusions: Acute cerebellar ataxia was the most frequent neurological complication, while encephalitis was associated with increased risk of neurological sequel. Direct presence of VZV-DNA was observed in patients with meningitis, while acute cerebellar ataxia and encephalitis were a result of an immune response.

The presented results serve as a reminder of the potential severity of chickenpox in unvaccinated, otherwise immunocompetent children.

KEY WORDS:

chickenpox, pediatric, varicella-zoster virus, sequels.

INTRODUCTION

Varicella-zoster virus (VZV) is an α-herpesvirus found exclusively in humans, known as the aetiological factor of an acute febrile exanthematous illness (varicella or chickenpox), usually linked with childhood. Although the disease is commonly considered benign, VZV has the potential to cause a wide range of different complications, including central nervous system (CNS) manifestations, such as encephalitis, meningitis, cerebellitis, myelitis, stroke-related

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syndromes, and Ramsay Hunt syndrome. Despite the administration of antiviral treatment, the complications are associated with considerable morbidity and mortality [1, 2].

In children, these complications are most often related to the primary infection, whereas in adult patients CNS manifestations are frequently reported to be a consequence of reactivation from latent-form VZV established in cranial and spinal ganglia [3-8].

Herein we present a single-centre retrospective study to assess the clinical, neuroimaging, and electroencephalographic features of children suffering from acute cerebellar ataxia, meningitis, and encephalitis as a challenging course of primary VZV infection and evaluate the correlation between clinical parameters and outcome of the disease.

MATERIAL AND METHODS

Of 484 children admitted to the Department of Infectious Diseases and Child Neurology between January 2009 and December 2018 due to chickenpox, 48 aged 17 months to 16 years, developing acute cerebellar ataxia, meningitis, or encephalitis associated with VZV infection were incorporated in the study group. Patients were identified using the International Statistical Classification of Diseases 10th Revision (ICD-10). Hospital charts were reviewed for signs and symptoms indicative of the above diagnosis with inclusion criteria shown in Table 1. In each case the collected data were as follows: age, sex, symptoms at hospital admission and discharge, length of hospital stay, results of clinical, laboratory, radiological, and neurophysiological studies, and neurological assessment throughout the time of hospitalisation. The collected data were extended to include the results of a post-hospitalisation survey containing questions regarding the neurological sequel, i.e. the quality of development after diagnosis, the occurrence of epileptic seizures and indications for antiepileptic treatment, and the need for neurological and psychological ambulatory care.

Patients were stratified into 3 groups according to the final diagnosis: (1) acute cerebellar ataxia, (2) acute aseptic meningitis, and (3) encephalitis, associated with acute VZV infection.

None of the patients in the study group was vaccinated against VZV. All patients included in the study were immunocompetent.

Laboratory tests were performed on standard analysers. CSF analysis included general assessment with reference values as follow: pleocytosis ≤ 5/µl, protein 15-45 mg/dl, and glucose 45-85 mg/dl, followed by PCR evaluation for VZV-DNA (Real-Time PCR, Qnostic VZV Analytical Panel, test sensitivity: 1000 copies/ml).

STATISTICAL ANALYSIS

Categorical data were given as numbers of cases and percentages; continuous variables were reported as mean, median, and range. The normality of the analysed data was evaluated by the Shapiro-Wilk test. The χ^2 test, Fisher exact test, and Kruskal-Wallis *H* test were performed to assess the relationship between categorical variables, and the Mann-Whitney *U* test and Student's *t*-test were used for quantitative variables. A p-value ≤ 0.05 was considered statistically significant.

All analysis was carried out using Statistica software version 13 (StatSoft Inc.)

ETHICS STATEMENT

The study was approved by the Bioethics Committee (Protocol No. 1235/18 of 6 December 2018).

RESULTS

Of 484 patients with a complicated course of primary VZV infection and indication for hospital admission, 48 met the inclusion criteria (9.9%). The cause of hospitalisation of the remaining 436 patients was the aggressive course of chickenpox with high fever, multiple lesions, and non-neurological complications with bacterial superinfections, inflammation of the lower respiratory tract, and gastroenteric symptoms.

Patients in the study group were significantly older (mean age: 5.22 ±2.8 vs. 3.95 ±3.6, p = 0.000238) and had

TABLE 1. Definitions and diagnostic criteria of the clinical syndromes

Acute cerebellar ataxia (ACA)	An inflammatory syndrome characterised by acute onset of cerebellar signs/symptoms (ataxia, dysmetria or nystagmus) often accompanied by vomiting, headache or fever, following the appearance of the typical chickenpox rash
Acute aseptic meningitis (AAM)	≥ 2 of following: fever > 38°C; meningeal signs; headache; nausea/vomiting plus • Pleocytosis with leucocytes > 5/µl • Negative CSF bacterial culture • No signs of brain parenchymal involvement
Encephalitis	≥ 2 of following: fever > 38°C; pleocytosis with leucocytes > 5/µl; abnormality in EEG; abnormal neuroimaging Signs of brain parenchymal involvement: • Altered mental status or decreased consciousness • Focal neurological deficit • Seizures

TABLE 2. Patients characteristics and outcome

Characteristics	Study group $n = 48$	ACA $n = 28$	AAM $n = 10$	Encephalitis $n = 10$	p
Gender: males/females, *n* (%)	26 (54.2)/22 (45.8)	17 (60.7)/11 (39.3)	5 (50)/5 (50)	4 (40)/6 (60)	0.51[a]
Age, years					
Mean ± SD	5.2 ±2.8	4.8 ±2.5	5.2 ±3.9	6.5 ±2.1	0.046[b]
Median (IQR)	4.5 (3.4-5.8)	4.3 (3.2-5.6)	4.0 (3.4-4.8)	5.8 (5.2-7.9)	
Median time from the onset of exanthem to hospital admission, days (IQR)	7 (4-9)	7 (6-8.5)	3 (2-5)	11 (6-55)	0.008[b]
Median hospital stay, days (IQR)	10 (8-13.5)	9 (6.5-11)	10 (10-12)	25 (15-22)	
Hospital stay ≤ 7, *n* (%)	10 (20.8)	10 (35.7)	0	0	0.0001[b]
Hospital stay ≥14, *n* (%)	12 (25)	3 (10.7)	1 (10)	8 (80)	
Outcome, *n* (%)					
Cure	33/48 (68.7)	21 (75)	9 (90)	3 (30)	0.008[a]
Sequels	14/48 (29.2)	7 (25)	1 (10)	6 (60)	
Death	1/48 (2.1)	–	–	1 (10)	

[a]χ^2 test; [b]Kruskal-Wallis H test

a longer hospital stay (mean time in days: 12.7 ±11.7 vs. 9.5 ±10.6, $p = 0.00001$) than those hospitalised for other than defined neurological reasons.

A seasonal pattern typical for the temperate climate was noted, with the highest admission rate from October to April and an unusual decline in January.

Among 48 children included in the study, a similar proportion of cases was noted in males and females ($n = 26$, 54.2% and $n = 22$, 45.8%, respectively). The mean age of patients affected by one of the defined neurological complications was 5.2 years (IQR, interquartile range 3.4-5.7). The median hospital stay was 10 days, with 25% of the patients requiring hospitalisation longer than 14 days.

The incidence of a given type of neurological complications defined as acute cerebellar ataxia, meningitis, or encephalitis during VZV infections in the study group was age related, with ataxia being more common in the younger age group and encephalitis found more frequently in older children.

The majority of children in the study recovered from the disease despite the complications. Table 2 summarises the patients' primary characteristics.

ACUTE CEREBELLAR ATAXIA

Acute cerebellar ataxia (ACA) was the most frequent complication among patients in the study group, reported in 28 of 48 cases (58.4%). The median age of patients affected by cerebellar complication was 4.3 years (IQR 3.2-5.6 years), with the highest frequency of this diagnosis observed among children aged 1-5 years (18/28, 64.3%), followed by group aged 5-10 years (8/28, 28.6%), and only 2 cases in children above that age.

The most characteristic ACA symptom was broad-based gait in 22 of 28 patients (78.6%). Other common symptoms comprised balance disturbances and emesis (12/28, 42.8% each), fever (9/28, 32.1%), headache, and dysmetria, present in 8/28 each (28.6%). Tremor and nystagmus were noted with similar frequency (4/28, 14.3%). The least commonly observed symptoms were strabismus (2/28, 7.1%) and slurred speech (1/28, 3.6%).

The clinical severity of ataxia symptoms, evaluated as the quantity of signs/symptoms present in a single patient, was low, with a maximum of 3 symptoms noted in 16 (57.1%) children with ACA, moderate with 4 or 5 signs present in 9 (32.1%) patients, and severe in 3 (10.8%) children with 6 or more symptoms.

The median time at the onset of cerebellar symptoms was 7 days after the beginning of rash (range 1-24 days), which was apparently more prolonged than in the subgroup with AAM. The median hospital stay was 9 days (range 3-17 days), which was much shorter than in the encephalitis subgroup.

Lumbar puncture (LP) was performed in 6 children, showing pathological results of cerebrospinal fluid (CSF) in only one case with pleocytosis of 10 cells/µl, and protein and glucose within the normal range. The CSF PCR test for VZV-DNA was negative in this case.

Computed tomography (CT) was performed in 9 cases (32.1%), showing pathological findings in one case, i.e. generalised cerebellar oedema. Two patients underwent magnetic resonance imagining (MRI) with no abnormal results. An electroencephalogram (EEG) was performed in 4 cases, and all those tests were within the age norm.

In the case of lack of accepted consensus regarding the best management of children with ACA, treatment was tailored in each case independently based on local

experience. In all children, the use of antiviral therapy (acyclovir – 3 × 10 mg/kg IV) was implemented, and all but 4 patients in this subgroup were treated with dexamethasone (dose range 0.15-0.2 mg/kg IV) for a median time of 9 days (IQR 7-11).

ACUTE ASEPTIC MENINGITIS

Acute aseptic meningitis (AAM) was as frequent as encephalitis, reported in 10 of 48 cases (20.8%) in the study group. The median age of patients affected by this complication was 4.0 years (IQR 3.4-4.8 years), with the highest frequency of this diagnosis observed among children aged 3-5 years (8/10, 80%), no cases below that age, one patient aged 5 years, and one above the age of 10 years.

The most characteristic sign of AAM was positive meningeal signs (9/10), with nuchal rigidity being present in all those patients, and lower Brudzinski sign evident in 5.

Almost as frequently as above, in 8 of 10 cases, headache described by patients as the sharpest pain in life was noted. Fever above 38.5°C was present with a similar prevalence.

Another common symptom was vomiting reported by 7/10 patients. The least common was dizziness, which was reported by 2/10 children.

The median time since the onset of symptoms typical for VZV infection to hospital admission was 3 days (range 2-10 days), which was the shortest result among subgroups. The median time of hospital stay was 10 days (range 8-14 days).

Lumbar puncture was performed in 8 children, showing pathological results in 7. Their laboratory and clinical findings are summarised in Table 3. In the remaining 2 children, spinal tap was not performed due to contraindications (coagulopathy in one and massive vesicle eruption in the lumbar region in the other). In 3 cases, the presence of VZV-DNA was confirmed by the detection of viral genetic material in CSF with the PCR method.

Computed tomography was performed in all cases, showing no pathological findings.

In this group, no MRI nor EEG examinations were performed in any patient.

In all children, antiviral treatment (acyclovir – 3 × 10 mg/kg IV) was implemented with dexamethasone (0.15 mg/kg IV), diuretics (furosemide 1 mg/kg IV), supportive therapy, and bed rest.

ENCEPHALITIS

Encephalitis was as frequent as AAM, found as a final diagnosis in 10 of 48 cases (20.8%) in the study group.

The median age of patients with the diagnosis of encephalitis was 6.5 years (IQR 5.2-7.9 years) with 2 children aged 3-5 years old (2/10, 20%), no case below that age, the highest frequency of this complication observed among children aged 5-10 years (70%), and one patient above the age of 10 years.

Patients in the encephalitis subgroup most commonly complained of persistent headache (90%), defined as the sharpest pain in their life, and showed signs of consciousness disturbances at different levels (70%). In this group, emesis was present in 7/10 patients; 50% complained of dizziness. Four patients showed signs of ataxia; the same number of children presented an epileptic attack of generalised tonic-clonic type. Fever in patients with encephalitis was observed in 30% only, and meningeal signs were present in 4 out of 10 patients.

The median time since the onset of typical vesicular rash to hospital admission was 11 days (range 6-55 days), which was the latest among the subgroups. The median time of hospitalisation was 19 days (IQR 15-22 days).

Lumbar puncture was performed in 9 children, showing pathological results in 5; laboratory and clinical

TABLE 3. Laboratory characteristics of CSF analysis and clinical results of patients tested

Main diagnosis		Meningitis ($n = 8$)	Encephalitis ($n = 9$)	p-value
Pleocytosis [cells/µl]	Mean ± SD	150.6 ±303.5	31.9 ±36.1	0.359
	Median (IQR)	19.0 (6.0-133.0)	21.0 (16.0-60.0)	
Protein [mg/dl]	Mean ± SD	25.1 ±10.5	22.5 ±10.7	0.961
	Median (IQR)	25.0 (15.5-29.5)	18.0 (16.0-32.0)	
Glucose [mg/dl]	Mean ± SD	57.4 ±16.0	55.0 ±11.6	0.957
	Median (IQR)	52.0 (48.0-60.0)	52.0 (48.5-64.0)	
Age, years	Mean ± SD	5.2 ±3.9	6.5 ±2.1	0.021
	Median (IQR)	4.0 (3.3-4.8)	5.8 (5.2-7.9)	
Time from the onset of symptoms to hospital admission, days	Mean ± SD	4.1 ±2.8	23.7 ±25.6	0.005
	Median (IQR)	3.0 (2-5)	11 (6-55)	
Hospital stay, days	Mean ± SD	10.6 ±1.7	25.1 ±21.5	0.0012
	Median (IQR)	10 (10-12)	19 (15-22)	

TABLE 4. CSF, neuroimaging, EEG findings and outcome of 10 children with encephalitis

Case	Age (years; sex)	CSF (cells/µl)	Radiology studies	EEG	Clinical findings	Outcome
1	7.4; F	60	MRI: extensive areas of the high cortex signal in T2-weighted and FLAIR sequences bilaterally in frontal, parietal, temporal and occipital region plus foci in left cerebellar peduncle with post-contrast enhancement	Normal	Nuchal rigidity, fever 40°C, emesis, headache, dizziness, diplopia, nystagmus, elevated mood	Hyperactivity
2	5.2; F	92	MRI: extensive areas of diffusion restriction (cytotoxic oedema) in right occipital and parietal lobes, ipsilateral parietal-frontal border and the posterior part of the thalamus in DWI sequences, increase of signal intensity in the T2-weighted and FLAIR sequences of this region	Diffuse extreme slowing of the background with high amplitude	Lethargy, emesis, headache, GTCS, left-sided paresis	Died
3	5.5; F	2	CT: brain oedema	Slowing of the background with high amplitude	Ataxia, aphasia, emesis, headache, dizziness, nystagmus	Psychomotor retardation
4	8.6; M	80	CT: normal	Slowing of the background	Nuchal rigidity, ataxia, absence seizures, lethargy, emesis, headache, dizziness, nystagmus, scanning speech	Cure
5	6.2; F	1	CT: hypodense foci on the border of the knee, inner capsule and part of the thalamus MRI: increased signal in T2-weighted and FLAIR sequences in the area of the inner capsule and cerebral peduncles with post-contrast enhancement	Normal	Aphasia, emesis, right-sided facial palsy central type, hyperactivity, short-term memory disturbances	Disturbances in short-term memory
6	10.4; F	25	CT: normal MRI: normal	Normal	Visual, auditory and olfactory hallucination, emesis, headache, dizziness, anisocoria	Cure
7	5.3; M	21	MRI: post-inflammatory gliosis	Normal	Brudzinski sign, ataxia, emesis, dizziness, peripheral paresthesia	Balance disturbances
8	3.8; M	n/d	CT: brain oedema MRI: hyperintensity of the cerebral grey matter in T2-weighted sequences	n/d	Brudzinski sign, fever 39°C, emesis, headache, apathy, irritation	Cure
9	4.3; M	1	CT: normal MRI: normal	Asymmetry of the background	Absence seizures, fever 38.5°C, temporal blindness, headache	Hyperactivity
10	7.9; F	5	MRI: high signal in T2-weighted and PD sequences bilaterally of the cortex of the temporal and occipital lobe with signs of oedema	Ictal changes (sharp wave–slow wave complexes)	Ataxia, GTCS, headache, hyperactivity, left-sided facial palsy central type, left-sided positive Babinski sign, right-sided paresis	Epileptic seizure

n/d – not done; GTCS – generalised tonic-clonic seizures

findings are summarised in Table 3 and 4. One patient disqualified from the procedure had signs of cerebral oedema as contraindications, followed by a lack of consent for LP in the following days. In 4 children, active inflammation in CNS was confirmed by the detection of oligoclonal bands in CSF; one of those children had a typical result of CSF general analysis. VZV-DNA was not found in the CSF of any of those patients. In 2 children, anti-VZV antibodies were detected – in IgM and IgG class in one, and in IgG class only in the other.

Neuroimaging studies were performed in all patients in this subgroup: in 6 patients in the form of CT, in 8 – MRI,

and in the case of 4 children, both methods were used. As a result, 3 CT tests (50%) showed pathological findings: in 2 in the form of cerebral oedema and in the latter as one-sided hypodensity areas of brain parenchyma on the border of the knee, inner capsule and anterior part of the thalamus in one.

Out of 8 children who underwent MRI, 6 (75%) had abnormal results:

- increased signal in T2-weighted and FLAIR sequences in the area of the inner capsule and cerebral peduncles with post-contrast enhancement in one case (Figure 1A),
- extensive areas of diffusion restriction due to cytotoxic oedema within the right occipital and parietal lobes, ipsilateral parietal-frontal border, and the posterior part of the thalamus visible in DWI sequences, with a discrete increase of signal intensity in the T2-weighted and FLAIR sequences of this region in one case (Figure 1B),
- extensive areas of the high cortex signal in T2-weighted and FLAIR sequences located bilaterally in the area of the frontal, parietal, temporal, and occipital region as well as a focus in left cerebellar peduncle with post-contrast enhancement in one case (Figure 1C),

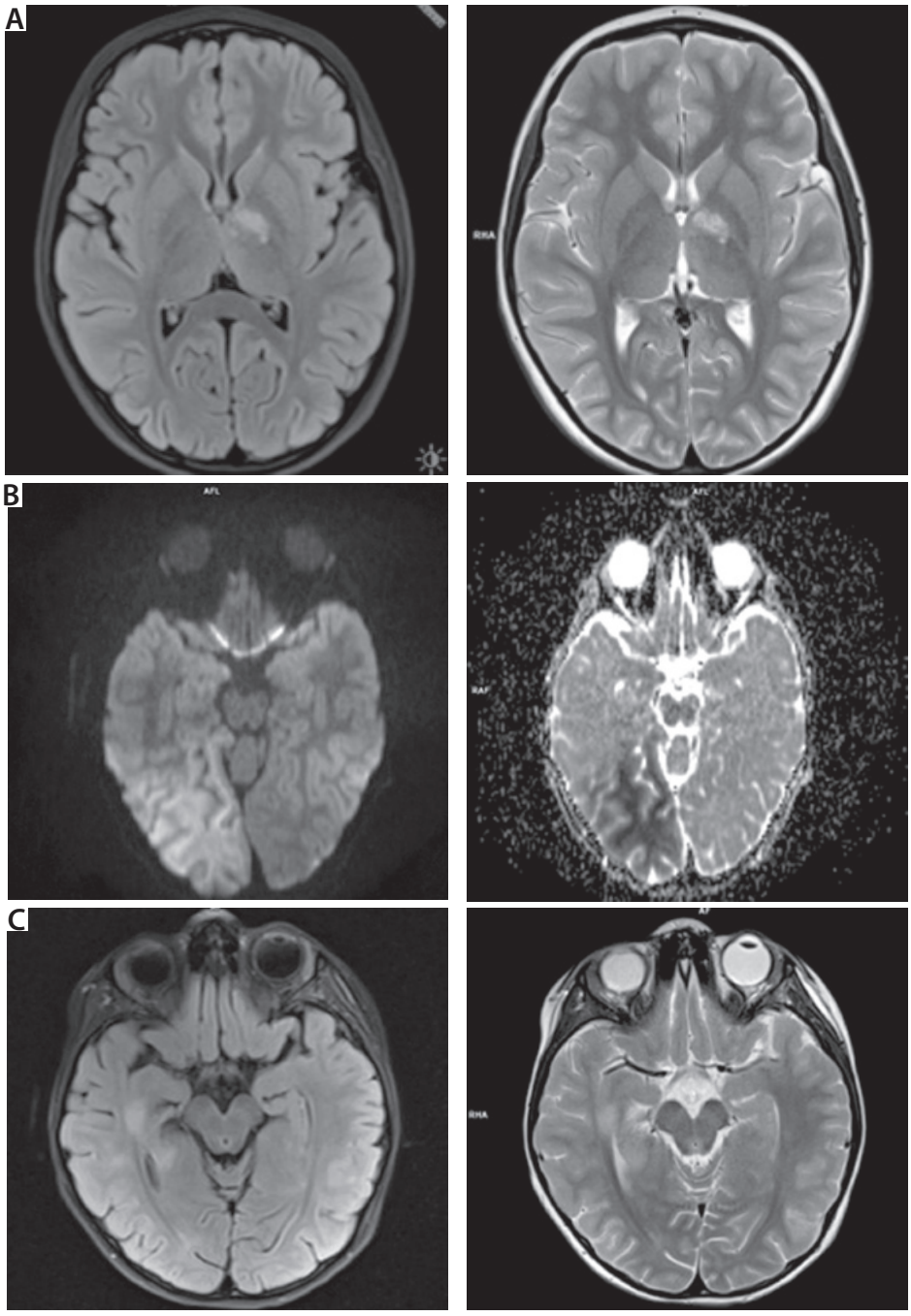

FIGURE 1. A) Increased signal in FLAIR (a) and T2-weighted (b) sequences in the area of the inner capsule and cerebral peduncles. **B**) Extensive areas of diffusion restriction due to cytotoxic oedema within the right occipital and parietal lobes and parietal-frontal border best visible in DWI1000 and ADC sequences. **C**) Extensive areas of the high cortex signal in T2-weighted and FLAIR sequences located bilaterally in the area of the frontal, parietal, temporal and occipital region

TABLE 5. The outcome in studied patients

Factor	With sequelae, *n* (%)	Without sequelae, *n* (%)	*p*-value
Sex			
Male	7 (46.7)	19 (57.6)	0.482[a]
Female	8 (53.3)	14 (42.4)	
CSF result ($n = 21$)			
Abnormal	4 (40)	9 (81.8)	0.0635[b]
Normal	6 (60)	2 (18.2)	
CT result ($n = 25$)			
Abnormal	2 (28.7)	2 (11.1)	0.0651[b]
Normal	5 (71.3)	16 (88.9)	
MRI result ($n = 10$)			
Abnormal	5 (83.3)	1 (25.0)	0.285[b]
Normal	1 (16.7)	3 (75.0)	
EEG result ($n = 13$)			
Abnormal	4 (44.4)	1 (25.0)	0.506[b]
Normal	5 (55.6)	3 (75.0)	
Final diagnosis			
ACA	7 (46.6)	21 (63.6)	0.008[b]
AAM	1 (6.6)	9 (27.3)	
Encephalitis	7 (46.6)	3 (9.1)	

[a]χ^2 test; [b]Fisher exact test

- high signal in T2-weighted and PD sequences bilaterally of the cortex of the temporal and occipital lobe with signs of oedema in one case,
- hyperintensity of the cerebral grey matter in T2-weighted sequences in one case
- and post-inflammatory gliosis in the last.

An electroencephalogram (EEG) was performed in 9 cases, showing abnormalities in the form of diffuse slow activity in 5 patients.

In the 50% of the patients of the encephalitis subgroup, CSF general analysis showed pathology. The other half required a complementary examination in the form of neuroimaging and electroencephalographic studies to confirm the diagnosis.

Among patients with abnormal MRI results, EEG was performed in 5 cases, showing anomalies in 2 children. Of children with an abnormal CSF general analysis, only one showed no deviations in the other tests.

Taking into account the 3 types of tests used (EEG, MRI, and CSF analysis), in the group of children diagnosed with encephalitis, 5 showed deviations in a single test, 4 in 2 types of tests, and one in all of the above-mentioned.

In all children, the use of antiviral treatment based on intravenous acyclovir (acyclovir – 3 × 10 mg/kg IV or 14 days) was implemented.

OUTCOME

Neurological sequelae were noted in 15 cases. Balance disturbances and mild atactic signs were reported in 7 patients with acute cerebellar ataxia, and one with encephalitis. Sequels found among children with encephalitis were as follows: mild behavioural changes, i.e. hyperactivity in 2 patients, and each of the following in one patient: psychomotor retardation, disturbances in short-term memory, and epileptic seizure. One patient with the diagnosis of acute aseptic meningitis suffered from prolonged headaches that resolved within 2 months. One child with a suspected inborn error of metabolism diagnosed with encephalitis succumbed after prolonged hospitalisation with multiorgan dysfunction.

The outcomes and comparison of clinical results of patients are shown in Table 5. No difference in terms of neurological sequelae were observed in relation to gender, CSF analysis, EEG test, or neuroimaging with the presence of sequelae ($p > 0.05$).

We found that the type of clinical manifestation and diagnosis of encephalitis were associated with a higher risk of neurological sequelae at the moment of discharge (odds ratio [OR] = 8.75, 95% confidence interval [95% CI]: 1.84-41.69; $p = 0.008$).

DISCUSSION

The 9.9% incidence of CNS complications in hospitalised children with chickenpox in this study is in line with the wide range of prevalence (8.1% to 25.4%) reported previously [3-8]. The differences among studies may depend on populations' sociodemographic structure (age, comorbidity, etc.) and hospitalisation policies as well as study assumptions. The seasonal incidence, typical for a temperate climate, seen in the study period is commonly observed by other authors [8, 10-12].

The median age of 4.5 years among children affected by any defined neurological complications in this study corresponds well with referential data [3-8, 11, 13-15]. Interestingly, patients hospitalised for CNS complications were considerably older than those admitted with other varicella-related complications (median age 3.3 years). The hypothesis of a specific postinfectious immune response as a possible reason for CNS complication might explain this trend. Older, and hence more immunocompetent, children are considered more susceptible to antibody-mediated inflammatory reactions.

Patients with a final diagnosis of acute cerebellar ataxia, a well-known complication of varicella in children occurring in 1 per 4000 children with VZV infection [16], were the most numerous subgroup, which is consistent with referential data [3, 5, 8, 15]. Encephalitis is the most severe common CNS complication during VZV infection, reported by some authors to be the most frequent viral cause of encephalitis, identified in children more often

than HSV [9, 17]. In our study 20.8% of children were diagnosed with encephalitis, and that prevalence is in line with available data [1-5, 12, 13].

Meningitis is another common manifestation of a complicated course of VZV infection; the proportion in our study was slightly lower than those found in published reports [3, 13, 18]. However, as reported by other authors, children with VZV-inducted meningitis tend to be younger than patients with encephalitis, and we confirmed this trend in our study [9, 19].

Regarding the onset of symptoms, children with acute cerebellar ataxia and encephalitis were admitted to the hospital later than children with acute aseptic meningitis. This case, as well as the fact that the only positive results of PCR for VZV were obtained in the acute aseptic meningitis subgroup, is in accordance with the hypothesis about postinfectious, immunological pathology of encephalitis and acute cerebellar ataxia and probable primary infectious origin of acute aseptic meningitis.

The median hospital stay of 10 days is consistent with data found by other authors [3-8, 11-13]. Most patients were diagnosed with ACA and needed steroid therapy for a median of 9 days, which might be a reason for prolonged hospitalization. The comparative analysis of subgroups with AAM and encephalitis showed differences in age and time to hospital admission and the length of hospital stay. Children with the diagnosis of AAM were hospitalized for a mean of 10.6 days, while the diagnosis of encephalitis resulted in the necessity of hospital stay prolonged to a mean of 25.1 days ($p = 0.002$). This finding is related to the fact that the immune system pathological activity induced by VZV infection leads to more extended and severe clinical presentation and a prolonged hospital stay.

No statistically significant differences were found in the results of the CSF general analysis between the subgroups of AAM and encephalitis. CSF pleocytosis was absent in 4 of 9 samples in a subgroup of patients with encephalitis and in 1 of 8 children with AAM. Because inflammatory parameters tend to be higher in patients with meningitis than in those with encephalitis, the inflammatory response may be related to immune mechanisms protecting from parenchymal involvement [20, 21].

Neuroimaging was performed in all encephalitis patients, showing pathological changes in 70%, and this group was the only one in which abnormal results of brain MRI were found.

In the subgroup of ACA, only 1 in 9 CT tests performed showed cerebellar oedema as an abnormal result. In the AAM subgroup, all brain images taken using CT were deemed normal or showing pre-existing abnormalities, e.g. pineal cyst. Hence, radiological imaging provides an inconstant effect on the diagnosis of VZV encephalitis. Brain CT scans are generally unremarkable, which is potentially valuable for excluding alternative diagnoses as haemorrhage or tumour.

In contrast, several specific MRI abnormalities, like areas of high signal intensity on T2-weighted sequence at the grey-white matter junction and in the deep white matter, or abnormal enhancement, have been described in VZV encephalitis [3, 20, 22, 23]. In our study, the highest prevalence of abnormal MRI study results was in the encephalitis subgroup, with the anomalies described being consistent with available reports. Thus, especially in children with clinical signs of varicella-associated ACA, neuroimaging is usually unnecessary. In contrast, all patients with symptoms of parenchymal involvement or possible vasculitis require neuroimaging as an essential tool in identifying pathological lesions.

In our study, abnormal electroencephalogram results were evident in 5 of 9 patients with brain tissue involvement in the form of diffuse slow activity. In contrast, in cases of ACA, no anomaly was found. Although EEG findings in encephalitis are unspecific, the principal use of this method is to demonstrate cerebral involvement during the early stage of the disease. Another advantage of this method is the possibility of monitoring the patient's condition in the course of the disease, because improvement shown within the first days of hospitalisation carries a good prognosis. In contrast, lack of electroencephalographic progress indicates a less favourable outcome, as reported previously [23, 24].

None of the analysed clinical parameters and additional tests was found to be a potential predictor linked with the possibility of sequels in our study. However, children with encephalitis had a higher risk of neurological sequelae at the moment of discharge.

All the study group children were treated with aciclovir, which is in accordance with other reports on VZV-related CNS complications [3, 4, 22, 25]. Some authors suggest consideration of the use of aciclovir as mandatory in every patient with complicated infection of viral aetiology, despite no proven benefits having been described [26]. Similarly, most authors use steroids in complex cases of ACA, despite no clear accepted consensus existing. In our group, only 4 of 28 patients with ACA did not receive steroid therapy. Therefore, comparison with a control was impossible. Hence, speculation about when antiviral or steroid treatment would benefit the outcome is not feasible.

In conclusion, acute cerebellar ataxia is the most frequent neurological complication of VZV infection, while encephalitis is associated with increased risk of neurological sequel. Direct presence of VZV-DNA was observed in patients with meningitis, while ACA and encephalitis were the result of a triggered immune response.

DISCLOSURE

The authors declare no conflict of interest.

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