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Neurological performance after central nervous system complication of childhood chickenpox

Ocena odległych wyników leczenia ospy wietrznej przebiegającej z powikłaniami w obrębie ośrodkowego układu nerwowego u dzieci

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Abstract

Varicella-zoster virus is an exclusively human pathogen of an acute exanthematous illness usually linked with childhood. Although the disease is commonly considered benign, varicella-zoster virus bears the potential of causing a wide range of different complications, including central nervous system manifestations. In this paper, an assessment of long-term sequelae and the quality of life in a cohort of patients with neurological complications who survived an acute episode is discussed. We enrolled a total of 71 patients aged two months to 16 years with the diagnosis of varicella complicated by central nervous system disease into the study. Data were collected after their discharge from the hospital by mail and by telephone call interviews using standardised questionnaires. The time from the discharge to the filling of the survey varied between the patients, with a median time of 5.4 years. The collected data were analysed, and the results were compared with the literature. The diagnosis of ischaemic stroke and encephalitis was linked to the most unfavourable outcome, as opposed to acute cerebellar ataxia associated with the most favourable prognosis. Neuropsychological performance should be further monitored to prevent a decrease of independence in everyday performance.

Keywords: long-term sequelae, performance, childhood, chickenpox

Streszczenie

Wirus ospy wietrznej i półpaśca jest wyłącznie ludzkim patogenem, wywołującym wysypkową chorobę zakaźną wieku dziecięcego. Chociaż choroba ta uważana jest za łagodną, wirus może powodować wiele różnych powikłań, w tym objawy łączone z ośrodkowym układem nerwowym. W pracy omówiono ocenę odległych następstw i jakości życia w grupie pacjentów z powikłaniami neurologicznymi w przebiegu zakażenia wirusem ospy wietrznej i półpaśca. Do badania włączono 71 pacjentów w wieku od 2 miesięcy do 16 lat z rozpoznaniem ospy wietrznej powikłanej objawami ze strony ośrodkowego układu nerwowego. Dane zostały zebrane po wypisie ze szpitala drogą pocztową i telefoniczną za pomocą wystandaryzowanych kwestionariuszy. Czas od wypisu ze szpitala do wypełnienia ankiety różnił się między pacjentami, mediana czasu wynosiła 5,4 roku. Zebrane dane poddano analizie, a wyniki porównano z literaturą. Najmniej pomyślne wyniki wiązały się z rozpoznaniem udaru niedokrwiennego i zapalenia mózgu, najpomyślniejsze – ostrej ataksji móżdżkowej. Należy nieprzerwanie monitorować funkcje poznawcze pacjentów, aby zapobiec powikłaniom odległym w zakresie codziennego funkcjonowania.

Słowa kluczowe: następstwa odległe, wyniki leczenia, wiek dziecięcy, ospa wietrzna

INTRODUCTION

Varicella-zoster virus (VZV) is an exclusively human pathogen of an acute febrile exanthematous illness (varicella or chickenpox), commonly occurring in children. Although the vast majority of varicella cases in immunocompetent hosts are uncomplicated and self-limited, the potential of the virus to cause a wide range of complications must be stressed. The most common non-neurological complications include bacterial suprainfection of skin lesions and transient hepatitis. Neurological disturbances may also occur, though infrequently, among the complications of VZV infection. This group involves primarily central nervous system (CNS) manifestations, such as cerebellitis, meningitis, and the most significant, and potentially life-threatening, encephalitis and stroke-related syndromes.

The objective of this paper was to assess long-term sequelae and the quality of life in a cohort of patients with neurological complications who survived an acute episode.

MATERIALS AND METHODS

In the initial follow-up, we enrolled into the study a total of 71 patients with a mean age of 4.8 years (interquartile range, IQR: 3.2–5.7 years) and a similar proportion of cases in males and females (n = 38, 53.5%; and n = 33, 46.5%, respectively) with the diagnosis of varicella complicated by CNS disease. Among the enrolled patients, 11 of 71 refused to participate in the long-term follow-up, and one patient succumbed during prolonged hospitalisation with multiple complications. Data were collected after the discharge from the hospital by mail and by telephone call interviews using standardised questionnaires concerning general and neurological symptoms, current treatment, patients' return to school, and need for specialist care, including psychological outpatient care and developmental support.

The time from hospitalisation due to chickenpox to follow-up questionnaire was a median of 5.4 (min. 0.7; max. 10.2), and a mean of 5.2 (standard deviation, *SD* 2.7) years.

We used the Glasgow Outcome Scale (GOS) as the primary measure and defined favourable outcomes with a GOS score of 5 (Tab. 1) (Jennett and Bond, 1975). The authors assessed in collegial review the GOS score with the use of clinical data of eligible patients. Detailed data derived from the surveys are presented in Tab. 2.

Categorical data were given as numbers of cases and percentages, while continuous variables were reported as means, medians and ranges. All the analyses was carried out using the Statistica software version 13 (StatSoft Inc.).

Participants

With the use of the International Classification of Diseases, 10th Revision (ICD-10) codes, we identified the patients treated for neurological complications of VZV infection (n = 71) at the age of two months to 16 years at the Department of Infectious Diseases and Child Neurology, Poznan University of Medical Sciences, during the years 2009–2018. The patients included in the study group had the final diagnosis of acute central or peripheral nervous system diseases associated with VZV infection. The diagnosis of chickenpox was based on the characteristic and unquestionable picture of cutaneous vesicular lesions and associated clinical symptoms, causing no need for further molecular testing.

GOS score	Clinical meaning	Outcome	Patients, No. (%)
1	**Death**	Poor	1 (1.7)
2	**Neurovegetative state**; patient unresponsive and speechless for weeks/months	Poor	0
3	**Severe disability**; patient dependent on daily support	Poor	2 (3.3)
4	**Moderate disability**; patient independent in daily life	Poor	4 (6.7)
5	**Good recovery**; resumption of everyday life with minimal neurological and psychological deficits	Favourable	53 (88.3)

Tab. 1. Glasgow Outcome Scale (GOS) categories and outcomes in the patients included in the follow-up study

Convulsions	An involuntary contraction of muscles typically seen with seizure disorders; with other potential causes like meningitis, poisoning, hypoglycaemia, dyselectrolytaemia or head injury excluded
Facial palsy	Weakness of the facial muscles resulting from temporary or permanent damage to the facial nerve
Acute cerebellar ataxia	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	≥2 of following: fever >38°C; meningeal signs; headache; nausea/vomiting plus Pleocytosis with leucocytes >5/μL Negative cerebrospinal fluid 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
Ischaemic stroke	Acute neurological deficit or any alteration in the level of consciousness due to a sudden loss of blood circulation to an area of the brain, resulting in a corresponding loss of neurological function

Tab. 2. Definitions and diagnostic criteria of the clinical syndromes

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	Diagnosis					
Surveys sent/ returned (71/60)	Cerebellar ataxia ($n = 28$)	Convulsions ($n = 19$)	Meningitis ($n = 10$)	Encephalitis ($n = 11$)	Ischaemic stroke ($n = 3$)	Facial palsy ($n = 1$)
	28/27	19/14	10/8	11/7	3/3	1/1

Tab. 3. Distribution of diagnoses among the active participants of the study

Among a broad spectrum of nervous system diseases associated with chickenpox, the patients in the study group were categorised into several clinical syndromes based on the predominant neurological abnormalities. The inclusion criteria used as indicative of the above diagnosis are shown in Tab. 2. The detailed results of additional tests performed during the hospitalisation of the studied patients, including general analysis of cerebrospinal fluid, electroencephalography, and imaging tests including magnetic resonance tomography and computed tomography are the subject of other studies (Frąszczak et al., 2022a, 2022b).

Ethics

The study was approved by the Bioethics Committee at the Poznan University of Medical Sciences (No. 1235/18 of 6 December 2018).

RESULTS

Overall, 60 of 71 eligible patients were included in the study: 59 survivors (83.1%) and one patient (1.4%) whose death was related to VZV encephalitis. 98.3% ($n = 59$) of the patients enrolled in the study group had no chronic diseases, and an underlying medical condition in the form of Gastaut type epilepsy was reported in one child. The follow-up time from the discharge time to the filling of the survey varied between the patients, with a median of 5.4 years ($SD = 2.5$, IQR 2.8–7.9).

In the analysed group, the most frequently diagnosed complications included: cerebellar ataxia ($n = 27$, 45%), convulsions found in 14 patients (23.3%), meningitis in eight children (13.3%), encephalitis in six survivors (10%) and the single fatal case in our group (1.4%). Three children were diagnosed with ischaemic stroke (5%) and one with facial palsy (1.7%). Tab. 3 presents the exact distribution of diagnoses among the patients participating in the survey.

Long-term outcome

In total, 53 of 60 patients (88.3%) had a favourable outcome, 50 (83.3%) presented a full recovery. Seven children (11.7%) suffered from significant consequences: two (3.3%) experienced severe disabilities, four (6.7%) had disabilities of moderate degree, and one (1.7%) died (Tab. 1).

Of 60 participants who returned the study questionnaire, the most favourable outcome was noted in the group diagnosed with acute cerebellar ataxia, with all 27 patients

A

	Abnormal development	Neurological care	Psychological care	Epileptic seizures	Anti-epileptic medications
All patients ($n = 59$)[a]	10 (16.9%)	16 (27.1%)	7 (11.8%)	4 (6.8%)	4 (6.8%)
Cerebellar ataxia ($n = 27$)	0	0	0	0	0
Convulsions ($n = 14$)	3 (21.4%)	6 (42.8%)	2 (14.3%)	2 (14.3%)	2 (14.3%)
Meningitis ($n = 8$)	1 (12.5%)	2 (25%)	2 (25%)	0	0
Encephalitis ($n = 6$)	3 (50%)	5 (83.3%)	2 (33.3%)	1 (16.7%)	1 (16.7%)
Ischaemic stroke ($n = 3$)	3 (100%)	3 (100%)	1 (33.3%)	1 (33.3%)	1 (33.3%)
Facial palsy ($n = 1$)	0	0	0	0	0

Data are No. with sign (%).
[a] One patient with an unfavourable outcome is not included.

B

Signs	All patients with abnormal development ($n = 10$)
Concentrating difficulties	3/59 (5.1%)
Behavioural issues	2/59 (3.4%)
Speech disorders	1/59 (1.7%)
Memory impairment	2/59 (3.4%)
Limb paralysis	3/59 (5.1%)
Motor deficit	1/59 (1.7%)
Seizures	4/59 (6.8%)
Data are No. with sign/total No. (%).	

*Tab. 4 A and B. Data derived from surveys (**A**) and persisting symptoms in 10 patients with abnormal neurodevelopment (**B**)*

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Clinical diagnosis	Patients, No (%)	Age, median (range)	Male – female ratio	Unfavourable outcome: GOS score <5 (%)	Favourable outcome: GOS score 5 (%)	Full recovery (%)	VZV-related deaths
Cerebellar ataxia	27 (45)	4.4 (1.7–12.7)	1.7	0	27 (100)	27 (100)	0
Convulsions	14 (23.3)	2.9 (0.4–8.2)	1.3	0	14 (100)	12 (85.7)	0
Meningitis	8 (13.3)	4.0 (3.3–5.0)	1	0	8 (100)	7 (87.5)	0
Encephalitis	7 (11.4)	5.3 (3.8–10.5)	0.75	4 (57.2)	3 (42.8)	3 (42.8)	1
Ischaemic stroke	3 (5)	4.3 (2.5–5.5)	2	3 (100)	0	0	0
Facial palsy	1 (1.7)	3.6	-	0	1 (100)	1 (100)	0

Tab. 5. Demographic features of the patients enrolled in follow-up

(100%) reporting an absence of neurological sequelae (Tabs. 4 and 5). The same result was noted in one patient diagnosed with facial nerve palsy.

The spectrum of persisting symptoms reported by the caregivers of the children included in the study was wide. The most severe, in the form of motor deficit (1.7%) and limb paralysis (3.4%), were linked to the diagnosis of ischaemic stroke and encephalitis. Other symptoms included behavioural (3.4%) and speech disorders (1.7%), difficulties concentrating (5.1%), and memory impairment (3.4%). The most common among persisting symptoms were epileptic seizures, present in 6.8% of the respondents. The above sequelae were noted in the patients diagnosed with encephalitis (n = 1, 14.3%), ischaemic stroke (n = 1, 33.3%), meningitis (n = 1, 12.5%), and convulsions (n = 1, 7.1%), and were the reason of seeking psychological care.

Of all patients who answered the study questionnaire, 10 showed abnormalities in neurodevelopment. The typical diagnoses among them included ischaemic stroke, encephalitis, and convulsions. Persisting symptoms among the patients varied from limb paralysis and tractable seizures to speech disorders, memory impairment and trouble concentrating. Detailed data are presented in Tabs. 4 A and B.

Among 14 analysed patients with convulsions as the cause of hospitalisation who returned the survey, six (42.8%) needed further neurological care, and two of them also required psychological support. One of those patients had a diagnosis of epilepsy before a seizure attack during chickenpox. One child was ultimately diagnosed with epilepsy. Among the remaining 12 children in this group, convulsions causing the need for hospitalization in the course of chickenpox were the only seizure episode until the completion of the questionnaire.

In the group of patients diagnosed with meningitis, the outcome was favourable in all eight patients (100%), with the GOS score of 5, however mild neuropsychological abnormalities in the form of behavioural issues were noted in one patient.

The highest percentage of unfavourable disease outcomes was observed in patients diagnosed with encephalitis and ischaemic stroke. The sequelae found among the children with VZV-related encephalitis were present in the form of unilateral paresis in one patient, focal epilepsy in another, and hyperactivity with attention deficit and short-term memory disturbances in yet another child. The only fatal case in the study was recognised as complicated encephalitis. In the group of three children diagnosed with ischaemic stroke, all reported severe effects were in the form of residual hemiparesis, with only one assessed as a minimal abnormality. Above motor dysfunction in the case of one participant post-hospital diagnosis of focal epilepsy was made, with a need for multi-drug therapy.

DISCUSSION

In this study, we assessed the outcome in patients with neurological complications of childhood VZV infection. The median delay of 5.4 years between the onset of the disease and the follow-up allowed a wider overview of sequelae, as the initial time after acute illness is associated with a more rapid recovery.

To our knowledge, long-term studies analysing a wide range of possible CNS complications of VZV infection in children are lacking. The distribution of neurological sequelae of VZV CNS infections is poorly described, as there are very few follow-up studies, with most authors focusing on one clinical syndrome only, making comparisons difficult.

The analysis of obtained data suggests that the severity of reported sequelae is connected with the clinical syndrome diagnosed, with encephalitis and stroke episodes linked to the most complicated outcomes. This conclusion is in line with previous reports on viral encephalitis and vasculitis (Gilden et al., 2009; Mailles et al., 2012).

In their work, Fowler et al. (2010) described follow-up results after childhood encephalitis of different viral aetiologies with VZV among identified agents, showing personality changes, amnesia, troubles concentrating, and speech disorders as the most frequent sequelae. Similar results were reported in the French three-year follow-up study (Mailles et al., 2012). The most common neurological sequelae in the patients with VZV encephalitis included concentration problems and various motor deficits.

Cognitive impairment following CNS infections has previously been reported in patients with VZV encephalitis (Hokkanen et al., 1997; Mazur-Melewska et al., 2016; Widgren et al., 2021). Studies including neuropsychological assessment after VZV encephalitis in the long-term follow-up are lacking, but few existing analyses suggest substantial

neuropsychological deficits compared with the controls (Grahn et al., 2013; Pöyhönen et al., 2021).

There is an essential field for further exploration of vasculopathies associated with VZV CNS infections, as the link between VZV and stroke is suggested by recent data to might have a greater impact on stroke incidence than previously thought (Eleftheriou et al., 2020; Pavlakis and Gelbard, 2020).

The common notion suggests that VZV meningitis is a relatively benign condition without sequelae. In our study, we found only minor neurological sequelae in patients diagnosed with VZV inducted meningitis, which is consistent with that theory.

In our study group, the patients hospitalised for convulsions during childhood chickenpox did not show severe sequelae during the follow-up. It might be concluded that in this clinical scenario, varicella as a febrile disease triggered the disclosure of the predisposition for possible future diagnosis of epilepsy.

The authors of available studies agree that the diagnosis of acute cerebellar ataxia does not refer to invalidating problems at the follow-up, and our conclusions support that observation (Bozzola et al., 2014; Koturoglu et al., 2005; Rack et al., 2010).

The poor outcome after childhood encephalitis is a well-known effect, and severe and permanent sequelae are usually well-recognised (Marques et al., 2021; Zhang et al., 2020). Moreover, infections with herpesviruses, including VZV, may trigger autoimmune reactions leading to multiple neurological problems such as encephalitis, obsessive-compulsive or tic disorders (Figlerowicz et al., 2020).

It must be stressed, however, that less severe sequelae may remain unrecognised on standard paediatric examinations, leaving patients without sufficient follow-up and support. As those less evident symptoms may become a problem with age and increasing demands, causing issues affecting the individual's quality of life and independence in daily activities, close follow-up is a must.

Given that neurological complications following VZV infections appear to be more common than previously thought, with sequelae ranging from mild to severe, it would be of a great importance to discuss the introduction of routine VZV immunisation of infants in Poland.

In conclusion, it must be stressed that despite being rare among the neurological sequelae of VZV infection in children, ischaemic stroke and encephalitis are linked to potentially severe and long-term outcomes.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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