

A.P. Golub, O.K. Duda, Yu.O. Sukhov

Shupyk National Medical Academy of Postgraduate Education, Kyiv

CLINICAL AND LABORATORY FEATURES OF MEASLES MENINGITIS  
AND MENINGOENCEPHALITIS IN ADULTS

e-mail: gala.med@ukr.net

The purpose of our study was to systematize and analyze the clinical and laboratory features of measles meningitis and meningoencephalitis in adults who were inpatient treatment at the Kiev City Clinical Hospital No. 4 in the period 2006-2019. We examined 37 adult patients with measles complicated by meningitis or meningoencephalitis. Among the examined patients, there were 54% men (n=20) and 46% women (n=17). Young people aged 18 to 40 years prevailed (86.5%) among all the examined patients. Despite the fact that these measles complications are observed quite rarely, 0.5-1 per 1000 cases of the disease, their development aggravates the course of the disease, lengthening the duration of hospital stay. The nature of the central nervous system disorders statistically significantly depended on the time of patients' admission to the hospital ( $\chi^2=6.84$ ,  $\phi=0.43$ ,  $p=0.009$ ). Upon admission to the hospital, all patients had positive meningeal symptoms, which required a therapeutic and diagnostic lumbar puncture. Obtained results of the cerebrospinal fluid analysis showed the presence of lymphocytic pleocytosis was determined from 15 to 230 cells in 1  $\mu$ l, which indicated a different degree of severity of the inflammatory process, which depended on the nature of the central nervous system disorders.

**Key words:** measles, adults, complications, meningitis, meningoencephalitis.

А.П. Голуб, О.К. Дуда, Ю.О. Сухов

КЛІНІКО-ЛАБОРАТОРНА ХАРАКТЕРИСТИКА КОРОВИХ МЕНІНГІТІВ  
ТА МЕНІНГОЕНЦЕФАЛІТІВ У ДОРОСЛИХ

Метою нашого дослідження було систематизація та аналіз клініко-лабораторних характеристик корових менінгітів і менінгоенцефалітів у дорослих, які перебували на стаціонарному лікуванні у Київській міській клінічній лікарні № 4 в період 2006-2019 років. Обстежено 37 дорослих хворих на кір, ускладнений менінгітами або менінгоенцефалітом. Серед всіх обстежених хворих переважали особи молодого віку від 18 до 40 років (86,5%). Незважаючи на те, що дані ускладнення кору спостерігаються досить рідко 0,5-1 на 1000 випадків захворювання, їх розвиток обтяжує перебіг хвороби, подовжуючи терміни перебування хворих у стаціонарі. Характер ураження центральної нервової системи статистично значимо залежав від термінів надходження хворих в стаціонар ( $\chi^2 = 6,84$ ,  $\phi = 0,43$ ,  $p = 0,009$ ). У всіх хворих при надходженні до стаціонару визначалися позитивні менінгеальні симптоми, що вимагало проведення лікувально-діагностичної люмбальної пункції. Отримані результати аналізу ліквору: визначити наявність лімфоцитарного плеоцитоза від 15 до 230 клітин в 1 мкл, що свідчило про різного ступеня вираженість запального процесу, який залежав від характеру ураження центральної нервової системи.

**Ключові слова:** кір, дорослі, ускладнення, менінгіт, менінгоенцефаліт.

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Measles is one of the most contagious diseases among the respiratory group of infections (the contagiousness rate is 90-98%). According to the WHO, 9 out of 10 contacts may develop the disease in the presence of contact with a patient with measles due to the lack of protective antibodies against the measles virus in the human body [1, 7, 10].

A patient with any of the clinical forms of measles is the source of infection [1]. The most severe complications that can occur in adults with measles are complications from the nervous system. The incidence of neurological complications in measles is 0.5-1 per 1000 cases [3, 5]. In contrast to neurological complications in other viral infections (herpesvirus, enterovirus infections, mumps, etc.) [2, 8], the available literature over the past decade is presented by scientific researches that describe isolated cases of nervous system disorders in adults with measles [3, 5, 6, 9].

**The purpose** of this study was to systematize and analyze the clinical and laboratory characteristics of measles meningitis and meningoencephalitis in adults, as well as the need to draw the attention of doctors of various specialties, primarily family doctors, neurologists, and infectious diseases specialists to these rare but rather severe complications of measles in adults.

**Materials and methods.** In the period of 2006-2019, 37 patients were treated with various degrees of the clinical symptoms severity of central nervous system (CNS) disorders on the clinical basis of the Infectious Diseases Department in the Shupyk NMAPE at the Kiev City Clinical Hospital No. 4. Among the examined and treated patients, there were 20 men out of 37 patients (54%) and 17 women out of 37 (46%), aged from 18 to 62 years ( $M \pm \sigma$ :  $29.7 \pm 9.8$ ,  $Me = 27$ ,  $IQR$ : 23–32.5). The structure of CNS lesions in the examined measles patients was as follows: in 18 out of 37 patients (48.6%) had the development of aseptic meningoencephalitis, in 4 out of 37 (10.8%) – aseptic meningitis. A separate group included 15 out of 37

patients (40.5%), who were diagnosed with symptoms of meningism after a diagnostic and treatment puncture.

The clinical diagnosis of measles was made taking into account epidemiological data and the presence of clinical symptoms of measles: febrile fever, characteristic maculopapular rash and its spread stages, catarrhal phenomena from the upper respiratory tract, scleritis and conjunctivitis, Koplik spots detection [1, 7]. Neurological complications were diagnosed based on the presence of meningeal and/or cerebral syndromes, laboratory findings of cerebrospinal fluid analysis (determination of pleocytosis, biochemical analysis).

Laboratory confirmation of the diagnosis of measles was carried out in accordance with the order of the Ministry of Health of Ukraine dated July 4, 2006 No. 441 "Organization and implementation of immunological monitoring of infections that are controlled by the methods of specific prevention (diphtheria, tetanus, whooping cough and measles)". In all patients, the measles diagnosis was confirmed by the detection of anti-Ig M to the measles virus by enzyme-linked immunosorbent assay in the blood serum taken when patients were admitted to the hospital.

Statistical processing of the obtained data was performed using the Statistica 6.1 for Windows software package. Verification of compliance of the indices distribution to the Gaussian one was carried out according to the Kolmogorov–Smirnov test. To compare the indices in two independent groups, the Mann–Whitney U test was used, the Kruskal–Wallis H test of variance was used to compare the three groups. The presence and strength of statistical relationships for qualitative indices was calculated using contingency tables. The data are presented as  $M \pm \sigma$  (mean  $\pm$  standard deviation), Me – median, IQR: Q1–Q3 – interquartile range, RR – relative risk, and 95% CI – confidence interval.

**Results of the study and their discussion.** Analyzing the presented data from table 1, it can be seen that among the examined patients, young people aged 18 to 40 years prevailed, respectively, 32 out of 37 patients (86.5%). Our results correlate with the literature data [1, 4, 5]. The nature of CNS lesions in patients with measles did not depend on age and was characterized by the development of aseptic meningoencephalitis in 48.6% (18/37) of patients, aseptic meningitis – in 10.8% (4/37). Symptoms of meningism were diagnosed in 40.5% (15/37) of patients.

Table 1

**Age structure of the examined patients**

Age, years	Meningoencephalitis		Aseptic meningitis		Meningism		Total	
	abs.	%	abs.	%	abs.	%	abs.	%
18–30	10	27.0	2	5.4	11	29.7	23	62.2
31–40	4	10.8	2	5.4	3	8.1	9	24.3
41–50	2	5.4	–	–	1	2.7	3	8.1
51–60	1	2.7	–	–	–	–	1	2.7
< 61	1	2.7	–	–	–	–	1	2.7
Total	18	48.6	4	10.8	15	40.5	37	100

The examined measles patients with aseptic meningitis and meningoencephalitis mainly had a severe course of the disease in 14 out of 37 patients (37.8%) and moderate – in 8 out of 37 (21.6%), while the clinical picture of measles was typical in these patients [1, 4, 6]. It should be noted that in all 15 of 37 patients (40.5%) with symptoms of meningism, the disease was characterized by a moderate course.

The severity of CNS damage in patients with measles may correlate with the severity of intoxication and meningeal syndromes, focal neurological symptoms, and the level of impaired consciousness.

When analyzing the data obtained, attention was drawn to the fact that the vast majority of patients admitted to the hospital with measles – 81.0% (30/37) who started treatment at home, at the time of hospitalization already had clinical signs of CNS damage. However, in 7 out of 37 patients (19.0%), neurological symptoms manifested during their treatment in a hospital on the 7–9th day of disease. The terms of admission to the hospital are shown in table 2 below.

Table 2

**Terms of admission of the examined patients to the hospital**

Disease day	Meningoencephalitis		Aseptic meningitis		Meningism		Total	
	abs.	%	abs.	%	abs.	%	abs.	%
4–6	5	13.5	3	8.1	12	32.4	20	54.0
7–9	12	32.4	1	2.7	3	8.1	16	43.2
10–12	1	2.7	–	–	–	–	1	2.7
Total	18	48.6	4	10.8	15	40.5	37	100

Most patients with neurological symptoms (Table 2) were hospitalized on the 4–6th day of the disease (during the period of rashes), while 32.4% (12/37) of patients were diagnosed with symptoms of meningism, measles meningoencephalitis – in 13.5% of patients (5/37), and 8.1% (3/37) – aseptic meningitis. However,

starting from the 7th day of the disease (pigmentation period), clinical symptoms of measles meningoencephalitis developed in 37.8% (14/37) of patients.

Thus, the nature of the nervous system disorders statistically significantly depended on the timing of admission of patients with measles to the hospital ( $\chi^2=6.84$ ,  $\phi=0.43$ ,  $p=0.009$ ), and late admission, in turn, increases the likelihood of developing more severe complications from the central nervous system (RR=3.4, 95% CI: 1.15-10.09).

In patients with measles complicated by meningoencephalitis, in addition to meningeal syndrome, signs of focal lesions of the brain substance of various severity degrees were determined – asymmetry of tendon and patellar reflexes and impaired coordination of movements – in 83.3% (15/18), pyramidal disorders – in 66.6% (12/18) of patients. 50.0% (9/18) of patients had nystagmus, flattening of the nasolabial fold, tongue deviation.

Table 3

Clinical symptoms duration in the examined patients

Duration, (days)	Meningoencephalitis+aseptic meningitis, n=22	Meningism n=15	Groups Comparison, U; p
Fever	12.1±3.1*	8.4±0.5	25.5; 0.006
Prodromal phase	3.4±1.0	3.3±1.0	157.5; 0.82
Skin rashes	9.7±2.3	8.0±1.4	42.5; 0.08
Headache	7.8±2.7*	3.3±1.4	17.5; 0.001
Meningeal symptoms	6.8±3.6*	1.7±0.5	7.5; 0.001
Hospital treatment	17.6±6.3*	12.7±3.5	79.0; 0.007

Note: U – Mann-Whitney U test. \* – the difference is significant at a statistically significant level ( $p<0.05$ )

14 out of 37 patients (37.8%) had a history of chronic concomitant somatic diseases: hypertension and coronary heart disease – in 4 out of 37 patients (10.8%), rheumatoid arthritis – in 1 out of 37 (2.7%), chronic sinusitis – in 8 out of 37 (21.6%), chronic tonsillitis – in 5 out of 37 (13.5%), diabetes mellitus – in 3 out of 37 (8.1%).

According to the results of CSF analysis in patients with aseptic meningoencephalitis and meningitis, lymphocytic pleocytosis was determined from 15 to 230 cells in 1  $\mu$ l. The level of pleocytosis in the cerebrospinal fluid depended on the nature of CNS disorders ( $\chi^2_2=15.5$ ,  $p=0.001$ ), meningism indices –  $2.9\pm1.5$  cells per 1 ml (Me=3.0, IQR:1.0–4.0), for meningoencephalitis –  $55.7\pm62.0$  (Me=23.5, IQR: 17.0–78.5), for aseptic meningitis –  $55.7\pm51.5$  (Me=44.5, IQR: 14.0–108.75).

In 7 of 18 patients (38.8%) with aseptic meningoencephalitis, an increase in the protein level in the cerebrospinal fluid was recorded in the range of 0.99–0.165 g/l, while the glucose level corresponded to the normal range.

Indices of white blood cell and platelet levels in the blood at admission did not differ significantly and were  $6.7\pm3.1\times10^9$  and  $175\pm33.5\times10^9$ /l for the group of patients with measles meningoencephalitis and aseptic meningitis, and  $7.1\pm4.3\times10^9$ /l and  $165.1\pm40.2\times10^9$ /l (U=49.0,  $p=0.8$ ; U=32.0;  $p=0.5$ , respectively) for a group of patients with symptoms of meningism.

The inpatient treatment duration in the group of patients with CNS disorders was longer and amounted to  $17.6\pm6.3$  days compared to patients with measles with meningism symptoms –  $12.7\pm3.5$  days and was statistically significantly different (U=79.0;  $p=0.007$ ).

After the complex pathogenetic and symptomatic therapy, the vast majority of patients – 89.2% (33/37) were dismissed from the hospital in a satisfactory condition for further outpatient observation, and 10.8% (4/37) of patients with aseptic meningoencephalitis were transferred to the Neurological Department to continue treatment and rehabilitation.

According to a number of authors, the most severe course of measles encephalitis or meningoencephalitis was observed when they occurred in the catarrhal period of the disease [7, 9]. However, in most patients, CNS complications develop in the period of rashes, less often in the period of pigmentation and recovery, as a rule, 5-14 days after the onset of the rash [3].

In all examined patients in the prodromal period of measles, pronounced manifestations of intoxication syndrome were observed. Photophobia, persistent headache, and meningeal symptoms were also observed in 100% of patients in all comparison groups. Dizziness disturbed 55.5% (10/18) of patients with meningoencephalitis, 50.0% (2/4) with aseptic meningitis, and also 40% (6/15) with meningism symptoms. The results obtained coincide with the data of a number of authors [5, 6, 9] on the features of intoxication syndrome in patients with measles with clinical symptoms of CNS disorders.

Table 3 presents data on the duration of clinical symptoms in the examined patients. It was found that the duration of the febrile period of the disease was statistically significant in patients with aseptic meningoencephalitis and meningitis in comparison with patients with meningism symptoms was  $12.1 \pm 3.1$  and  $8.4 \pm 0.5$  days, respectively ( $U=25.5.0$ ;  $p=0.006$ ). Similar statistically significant changes were characteristic in the compared groups in the duration of headache ( $7.8 \pm 2.7$  and  $3.3 \pm 1.4$  days;  $U=17.5$ ,  $p=0.001$ ), as well as in the meningeal syndrome ( $6.8 \pm 3.6$  and  $1.7 \pm 0.5$  days;  $U=7.5$ ,  $p=0.001$ ).

It should be noted that neurological symptoms in the rashes period were more pronounced in patients with measles meningoencephalitis, manifested by signs of cerebrospinal fluid hypertension in 72.2% (13/18) of patients. In 61.1% (11/18) of patients in this group, impaired consciousness was noted: psychomotor agitation – in 22.2% (4/18), sopor – in 33.3% (6/18), coma of the 1st degree – in 5.55% (1/18) of patients. The described feature of the measles course in patients with CNS disorders during the period of rashes is also confirmed by the data of scientific literature [1, 5, 6, 7, 10].

### Conclusion

Our studies have shown that the examined patients with aseptic meningitis and meningoencephalitis had a predominantly severe course of the disease, especially in the presence of chronic concomitant pathology from the internal organs. Thus, the nature of the nervous system disorders statistically significantly depended on the timing of admission of patients with measles to the hospital ( $\chi^2=6.84$ ,  $\phi=0.43$ ,  $p=0.009$ ), and late admission, in turn, increases the likelihood of developing more severe complications from the central nervous system ( $RR=3.4$ , 95% CI: 1.15-10.09).

In the clinical picture in measles patients with meningism symptoms and patients with aseptic meningitis, intoxication and meningeal syndromes prevailed, and with the development of measles meningoencephalitis, cerebral focal symptoms appeared, which required a longer treatment in a hospital. It was found that the inpatient treatment duration in the group of patients with CNS disorders was longer and amounted to  $17.6 \pm 6.3$  days compared to patients with measles with meningism symptoms –  $12.7 \pm 3.5$  days and was statistically significantly different ( $U=79.0$ ;  $p=0.007$ ).

According to the results of the CSF analysis in patients with aseptic meningoencephalitis and meningitis, lymphocytic pleocytosis from 15 to 230 cells in  $1 \mu l$  were determined, indicating varying degrees of severity of the inflammatory process, and depended on the nature of the CNS lesion ( $\chi^2=15.5$ ;  $p=0.001$ ).

Thus, the awareness of doctors of various specialties in matters of the clinical and laboratory characteristics of measles meningitis and encephalitis in adults will allow timely verification of the diagnosis, and also start the necessary adequate therapy.

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