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Systemic manifestations in the course of meningococcal disease

Sistemske manifestacije tokom meningokokne bolesti

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Abstract

Background/Aim. Meningococcal disease most often manifests itself as meningitis or sepsis. During the course of these diseases, other clinical events sometimes develop such as pneumonia, pericarditis, arthritis, and they are referred to as extrameningeal or systemic manifestations of the meningococcal disease. The aim of this study was to investigate the type and the incidence of particular extrameningeal/systemic manifestations among patients with meningococcal meningitis and sepsis, including time of their onset and the influence on the disease outcome. **Methods.** The retrospective study of the medical records of 246 patients treated for meningococcal disease over the 25-year period in the Institute for Infectious and Tropical Diseases, Belgrade was conducted. The patients, aged 3 months to 82 years both sexes, were divided into two groups. **Results.** Out of 246 patients extrameningeal/systemic manifestations were found in 42 (17.1%) patients: 35 (14.2%) occurred during meningitis, and seven (2.8%) during sepsis. Pulmonary manifestations (mostly pneumonia) were the most prevalent, found in 12 (4.9%) patients, followed by heart involvement in nine (3.6%) patients (mostly pericarditis, in seven or 2.8% patients). Various ophthalmic manifestations occurred in seven (2.8%), arthritis in 4 (1.6%) and sinusitis in six (2.4%) patients. Otitis, multiple renal embolisms with hematuria, osteomyelitis and thrombophlebitis were evidenced in one patient, each. Most of the systemic manifestations (30 patients or 71.4%), developed within the initial three days of the disease ($p < 0.01$), suggesting direct pathogenic mechanism induced by meningococci *per se*, while only three (7.1%) developed after seven days, when immune-mediated disease was more likely. Even though these manifestations complicate and prolong treatment of the meningococcal disease, they had no major influence on the disease outcome. Lethal outcome occurred in 2 (4.76%) patients, both with the meningococcal type of the disease. **Conclusion.** Extrameningeal or systemic manifestations are uncommon complications during the course of both meningococcal meningitis and sepsis. The onset of pneumonia, pericarditis, eye involvement, and arthritis, within the initial seven days of the disease, were most prevalent in the course of meningitis. They had no major influence on the disease outcome.

Key words:
meningitis, meningococcal; sepsis; pneumonia; pericarditis; prevalence; treatment outcome.

Apstrakt

Uvod/Cilj. Meningokokna bolest najčešće se manifestuje kao meningitis ili sepsa. U toku ovih bolesti ponekad se razviju i neke druge kliničke manifestacije, takođe izazvane meningokokom, kao što su pneumonija, perikarditis, artritis i one se nazivaju ekstrameningealne ili sistemske manifestacije. Cilj rada bio je ispitivanje tipa i incidencije ekstrameningealnih ili sistemskih manifestacija među bolesnicima sa meningokoknim meningitisom i sepsom, i utvrđivanje vremena njihovog nastanka i njihovog uticaja na ishod bolesti. **Metode.** Urađena je retrospektivna studija medicinske dokumentacije 246 bolesnika lečenih od meningokokne bolesti u toku 25 godina u Institutu za infektivne i tropske bolesti u Beogradu. **Rezultati.** Od 246 bolesnika čija dokumentacija je obrađena, ekstrameningealne ili sistemske manifestacije registrovane su kod 42 (17,1%) bolesnika. Od toga, 35 (14,2%) nastalo je tokom meningitisa, a sedam (2,8%) za vreme sepse. Plućne manifestacije, najčešće pneumonija, nađene su kod 12 (4,9%) bolesnika, a zatim kardiološke kod devet (3,6%) i to najčešće perikarditis (kod sedam ili 2,8%) bolesnika. Različite oftalmološke manifestacije nađene su kod sedam bolesnika (2,8%), artritis kod četiri (1,6%) i sinuzitisi kod šest (2,4%) bolesnika. Otitis, multiple bubrežne embolije sa hematurijom, osteomijelitis i tromboflebitis nađeni su kod po jednog bolesnika. Najveći broj sistemskih manifestacija, 30 ili 71,4% nastao je u prva tri dana bolesti ($p < 0,01$), što govori u prilog direktnom dejstvu meningokoka, dok su samo tri (7,1%), nastale posle sedam dana, kada se mogu pretpostaviti imunološki posredovani mehanizmi bolesti. Mada su ove manifestacije komplikovale i produžile lečenje od meningokokne bolesti, one nisu značajnije uticale na ishod bolesti. Letalni ishod nastupio je kod 2 bolesnika sa meningitisom (4,7%). **Zaključak.** Ekstrameningealne ili sistemske manifestacije su retke komplikacije u toku meningokoknog meningitisa i sepse. Nastanak pneumonije, perikarditisa, očnih manifestacija i atrtritisa najčešće se registruje u toku prvih sedam dana bolesti, češće u toku menigitisa i ne utiče na ishod bolesti.

Ključne reči:
meningitis, meningokokni; sepsa; pneumonija; perikarditis; prevalenca; lečenje, ishod

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Introduction

The term meningococcal disease includes different clinical manifestations caused by *Neisseria meningitidis*. All manifestations of the infection are based on penetration and bloodborne dissemination of meningococcus, as well as on a wide range of pathophysiological events triggered by the bacterial endotoxin. The intensity of the inflammatory response induced by the endotoxin generally determines severity of the clinical presentation.

Meningococcal disease may present itself either as sepsis or meningitis. Transient meningococcemia, pharyngitis, pneumonia, pericarditis, arthritis and conjunctivitis are only infrequently diagnosed. These less frequent clinical conditions may be the only manifestations of the meningococcal disease, and in such cases the etiology may remain unconfirmed due to rapid recovery after favorable response to empiric antibiotic therapy. When these manifestations develop in the course of meningitis, they are referred to as extrameningeal, and systemic if in the course of sepsis.

Extrameningeal or systemic manifestations of the meningococcal disease most frequently occur in the early phase of the disease, which indicates that they develop as a direct consequence of meningococcal dissemination. Less commonly, they develop in the later phase, frequently at the very end of the antibiotic treatment, which is indicative of the immune-mediated nature of the event.

Extrameningeal or systemic manifestations most commonly involve the lungs, heart, joints and eyes. They prolong and complicate the treatment and may sometimes influence the outcome of the disease.

The aim of this retrospective study was to investigate the prevalence of extrameningeal and/or systemic manifestations among the patients with meningococcal meningitis and sepsis, as well as the time of their onset and influence on the course and outcome of the disease.

Methods

Medical records of patients treated for meningococcal disease at the Institute of Infectious and Tropical Diseases in Belgrade over the period 1979–2004 were analyzed.

The analysis included 246 patients of various ages (3 months to 82 years) and both sexes.

The patients were divided into two groups:

Group 1 – Meningitic type of the disease characterized by typical symptoms and signs, along with signs of inflammation in the cerebrospinal fluid (CSF), including pleocytosis of 100–2 000 polymorphonuclear leukocytes per cubic millimeter, low glycorrhachia and increased proteinorrhachia.

Group 2 – Septic type of the disease characterized by the presence of septic manifestations accompanied by excessive skin changes, without meningeal irritation and scarce CSF pathology (< 100 polymorphonuclear leukocytes per cubic millimeter, along with normal both glycorrhachia and proteinorrhachia).

At the beginning of the study period both pediatric and adult patients were included (patients age ranged from less than a year to over 80). Over the last 10 years, due to the reorganization of the pediatric service, we treated adult patients mostly.

The diagnosis of meningococcal disease was established by isolation of meningococci from the blood and/or CSF. Newer diagnostic techniques, such as polymerase chain reaction (PCR) were not available. Serotyping was not performed in all the cases, but serotype B prevailed, followed by serotypes C and A.

Diagnosis of extrameningeal and systemic manifestations was based on standard clinical diagnostic methods (chest X-ray, ECG, echosonography, pericardiocentesis if required, ophthalmological examination, etc).

All statistical analyses were performed using the electronic database organized in the SPSS (version 11.5) statistical package. The Chi-square test was used to assess the prevalence of certain extrameningeal and/or systemic manifestations of meningococcal disease in the meningitis versus septic group.

Results

The study series involved the total of 246 patients. Out of these, 211 (85.8%) had meningitis, while 35 (14.2%) were diagnosed with the sepsis.

Systemic manifestations were evidenced in 42 (17.1%) patients, out of which 35 (14.2%) and seven (2.8%) had meningitis and sepsis respectively. These manifestations were more frequent among patients with meningitis, but the difference did not reach the level of statistical significance ($p > 0.05$).

Among extrameningeal manifestations the most common were pulmonary, recorded in 12 (4.9%) patients, followed by cardiac in nine (3.6%), ophthalmic in seven (2.8%), articular in four (1.6%), maxillary sinusitis in six (2.4%), while otitis media, multiple renal embolisms with hematuria, osteomyelitis and thrombophlebitis were found in one (0.4%) patient each (Table 1).

The distribution of particular extrameningeal/systemic events did not differ among meningitis versus septic patients.

Pneumonia was the most prevalent pulmonary manifestation (ten patients) and most frequently found in the meningitis group (9/10 patients, $p < 0.05$) (Table 1).

Pericarditis was the most common cardiac manifestation (7/9 patients) and it was more frequent in the patients with meningitis (Table 1).

Ocular and auricular manifestations were recorded in seven and in four patients, respectively (Table 1).

Most of the systemic manifestations, 30 (71.4%), developed within the first three days of the disease, nine (21.4%) within 3–7 days, while only three (7.1%) developed after seven days. Difference between early onset (1–3 days) and late (> 7 days) reached the level of statistical significance ($p < 0.01$) (Table 2).

The average duration of treatment was eight days for the meningitis in comparison to 10 days for sepsis ($p > 0.01$). The treatment was significantly longer (15 days) in the group with extrameningeal manifestations ($p < 0.05$).

Table 1

Type and frequency of extrameningeal/systemic manifestations in the course of meningococcal disease

Type of complications	Extrameningeal/systemic complications [n(%)]		
	Patients with meningitis (n = 211)	Patients with septics (n = 35)	Total (n = 246)
Pulmonary	11 (5.2)	1 (2.8)	12 (4.9)
pneumonia	9 (4.3)*	1 (2.8)	10 (4.1)
bronchitis	1 (0.5)		1 (0.4)
atelectasis	1 (0.5)		1 (0.4)
Cardiac	7 (3.3)	2 (5.7)	9 (3.6)
pericarditis	5 (2.3)	2 (5.7)	7 (2.8)
transitory nodal rhythm	1 (0.5)		1 (0.4)
wandering pacemaker	1 (0.5)		1 (0.4)
Ophtalmic	6 (2.8)	1 (2.8)	7 (2.8)
optic nerve papilitis	1 (0.5)	1 (2.8)	2 (0.8)
epipapillary hemorrhage	1 (0.5)		1 (0.4)
papillary edema	2 (0.9)		2 (0.8)
conjunctivitis	2 (0.9)		2 (0.8)
Articular	3 (1.4)	1 (2.8)	4 (1.6)
arthritis of the knee	3 (1.4)		3 (1.2)
arthritis of the ankle		1 (2.8)	1 (0.4)
Maxillary sinusitis	6 (2.8)		6 (2.4)
Otitis media	1 (0.5)		1 (0.4)
Renal		1 (2.8)	1 (0.4)
Osteomyelitis		1 (2.8)	1 (0.4)
Thrombophlebitis	1 (0.5)		1 (0.4)
Total	35 (16.6)	7 (20)	42 (17.1)

* $p < 0.05$ *vs* patients with sepsis

Table 2

Time of onset of 42 extrameningeal/systemic manifestations during the course of menigococcal disease

Extrameningeal / Systemic manifestation	Number of patietns (%)		
	Day 1–3	Day 3–7	Day >7
Pneumonia	5 (11.9)	5 (11.9)	
Atelectasis		1 (2.4)	
Bronchitis	1 (2.4)		
Pericarditis	6 (14.2)	1 (2.4)	
Transitory nodal rhythm	1 (2.4)		
Wandering pacemaker	1 (2.4)		
Papillitis of the optic nerve	1 (2.4)		1 (2.4)
Epipapillary hemorrhage	1 (2.4)		
Papillary edema	2 (4.7)		
Conjunctivitis	2 (4.7)		
Arthritis	2 (4.7)	1 (2.4)	1 (2.4)
Thrombophlebitis		1 (2.4)	
Renal embolism with hematuria	1 (2.4)		
Osteomyelitis			1 (2.4)
Otitis media	1 (2.4)		
Sinusitis	1 (2.2)		
Total	30 / 71.4	9 (21.4)	3 (7.1)

The total number of lethal outcomes among the patients affected with meningococcal disease was 13 (5%), being higher among the patients with the septic type of the disease. Among patients with extrameningeal manifestations (n = 42) the outcome of the disease was favorable in 40 patients (95.2%), while 2 (4.76%) patients died (pneumonia and thrombophlebitis), both from the meningitis group.

Discussion

In the course of the meningococcal sepsis and meningitis, in addition to clinical manifestations typical for the disease, other extra-meningeal/systemic clinical conditions may develop, as well. In our series of patients, they developed in 17%. Etiology of the manifestations may be verified by isolation of meningococci and/or detection of the meningococcal DNA, however these tests are often negative since antibiotic therapy has already been initiated.

Regarding pulmonary manifestations, pneumonia was most frequently described, primarily in the elderly [1, 2]. It was also most common in our patients (4.1%), almost exclusively in those with meningitis (9 of 10). Pneumonia occurring in the course of the meningococcal disease may be induced by the meningococci *per se* or by some other organisms (due to aspiration during the course of meningitis). If the nasopharyngeal carriage of meningococci is present, identification of

the disease etiology may be unreliable if based on the sputum culture only, due to possible contamination of sputum samples. In our series, meningococci were isolated from the blood cultures, and pneumonia resolved within seven days in 9/10 patients, suggesting meningococcal etiology.

One patient with pneumonia which developed on the 6th day of meningitis died.

Primary meningococcal pneumonia is rather uncommon manifestation of the meningococcal disease. It develops most commonly in the immunocompromised or elderly patients [3]. In a study carried out in Finland, out of 182 patients with of community-acquired pneumonia, meningococcus was proved to be the causative organism in six cases only [3]. It may be preceded by viral respiratory infections. Among the majority of the elderly patients with meningococcal infections, Young et al. [4] reported serologic evidence of influenza.

Involvement of the paranasal sinuses and middle ear is most probably a consequence of the meningococcal infection *per se*, although the role of other bacteria cannot be ruled out. Sinusitis was evidenced in six patients, while otitis and lung atelectasis were found in one patient each (both with impaired state of consciousness during meningitis).

Cardiac manifestations most frequently described are pericarditis and myocarditis, while in our patient series, conduction disorders (transitory nodal rhythm and wandering pacemaker) were observed, as well.

Among patients with purulent pericarditis, meningococcal etiology was confirmed in 6–16% [5]. The prevalence of pericarditis of 2.8% in our series of patients is in concordance with the data reported by Morse et al. [6] and Pierce et al. [7] who recorded pericarditis prevalence of 3–19% among patients with the meningococcal disease.

Finkelstein et al. [5] proposed a classification of meningococcal pericarditis into three groups: pericarditis as local manifestation of the disseminated meningococcal disease; isolated meningococcal pericarditis; and reactive (immune-mediated) pericarditis.

Meningococcal pericarditis may be manifested as purulent or as serous. The difference is related to the time of its onset. Purulent pericarditis develops during the early, bacteremic phase, while serous pericarditis develops later in the course, even the convalescence phase (group three according to Finkelstein [5]). It is believed that bacterial antigens due to molecular mimicry lead to cross-reaction with the pericardial antigens.

Various meningococcal serotypes were confirmed among patients with pericarditis. It was observed that pericarditis developed more frequently in patients induced by serotype C (61%); serotype B was found in two pediatric patients, while serotype W135 was recorded in four adult patients [8, 9]. However, other authors reported the highest number of pericarditis, arthritis and pneumonia cases in the course of infections induced by serotype W135 [6, 7]. In our series of patients there was no difference in the distribution of meningococci serotypes regarding pericarditis. Clinical manifestations of the disease may be obvious (chest pain, dyspnea, pericardial friction rub). However, persistent fever was occasionally the only clinical sign. ECG abnormalities were found in all the patients, while the diagnosis was confirmed by echocardiography when available. Pericardial effusion evacuation is infrequently performed (due to small amount), and thus isolation of the meningococci is exceptionally rare. If the amount of effusion is large enough it may lead to cardiac tamponade, a life threatening condition [7]. Fortunately, there were no cardiac tamponade cases in our series.

In our series of patients, pericarditis was not associated with any organ-specific symptoms, and the diagnosis was established according to persistent fever and minimal pericardial effusion on echosonography, both of which completely resolved after the conservative treatment with the nonsteroidal anti-inflammatory drugs, while only one of them received glucocorticoides.

Recurrent pericarditis is exceptionally rare after the meningococcal infection. Several cases were described among children, while the reasons of its recurrence most commonly remain unknown [10–12]. The association with chronic inflammatory diseases, cardiac surgeries, influenza A infections or vaccinations was evidenced in some cases [13]. In these cases, the course of the disease may be chronic and unpredictable, regardless of the applied therapy or cause of the relapse. It is known that corticosteroids lead to rapid withdrawal of symptoms, however their administration may also induce dependance [14].

Based on the literature data, myocarditis of different degree of severity is found in even 50% of patients who had died from the meningococcal disease [15]. In a series of children with meningococcemia, higher incidence of lethal outcomes was observed in the group with echocardiographic signs of the myocardial dysfunctions and well as signs of myocardial ischemia with elevated values of creatine phosphokinase and troponin I [16, 17]. In our series of patients with pericarditis two had ECG findings of myopericarditis, which resolved after a day, but none of them had only myocarditis.

Congestive heart failure with pulmonary edema and high central venous pressure accompanied by the signs of poor peripheral perfusion were also described [18].

Arthritis developing in the course of meningococcal disease is uncommon occurring in 5–11% of patients [19, 20]. Arthritis may develop early, during dissemination of meningococci, or later, when immunological mechanisms are supposed to be involved (synovial precipitation of immune complexes). Jarret et al. [20] reported arthritis in 10–20% of patients, within 4–7 days from the onset of the disease. A large joint (most frequently the knee) is most commonly affected, while involvement of two or more large joints is less common. Weisfelt et al. [22] conducted a large national study to investigate the prevalence of arthritis among patients suffering from bacterial meningitis and they found it to develop most frequently in the course of meningococcal meningitis (48/697, 12%). The knee was affected in 50%, without any influence on favorable outcome of the disease or joint function.

Arthritis developed in four (1.6%) patients from our series and it affected one joint in each of them. In two patients, arthritis developed within three days from the onset of the

disease, while in one of the patients it developed after seven days (suggesting the immune-mediated mechanism). Etiology of the disease may be confirmed by isolation of meningococci and/or detection of its DNA in the synovial fluid. In our patients, diagnosis was based on the clinical criteria only. Some authors reported arthritis to be significantly more frequent in infection caused by the serotype W135 [6, 7].

Ophthalmic changes developing in the course of meningococcal disease may be diverse. In addition to conjunctivitis, which frequently accompanies numerous infectious diseases, deeper structures of the eye may also be affected. The most serious complication is endophthalmitis that may lead to loss of vision [23]. In the pre-antibiotic era, meningococcus was the most common cause of endophthalmitis and it developed in 5% of patients [24]. In our series ocular changes were found in seven (2.8%) and they developed most frequently within the first three days after the onset of the disease, being more frequent among the patients with meningitis. Conjunctivitis and epipapillary hemorrhage developed two days after the onset of the disease as a result of meningococcal dissemination. Papillary edema and the optic nerve papillitis developed in the course of meningitis due to the increased intracranial pressure. In one of the patients, papillitis of the optic nerve developed seven days after the onset of the disease, and thus, in addition to the infectious component the immune one may be also considered in this case [25].

Celulitis, adnexitis, sialoadenitis, upper respiratory tract infections, genital and anal infections were also reported as rare complications [26].

In our series of patients, we have also found complications that had never been previously reported before. Multiple renal embolisms with macroscopic hematuria associated with sepsis is most probably induced by activation of the vasoactive material due to edotoxemia. Osteomyelitis developed after extensive skin and soft tissue necrosis in a patient suffering from meningococcal sepsis.

Most of the extrameningeal/systemic manifestations developed within the first three days of the disease (71.4%) which undoubtedly suggests a direct influence of meningococci. The proposed immune-mediated events associated with meningococcal meningitis [9] are observed in only 3 (7.1%) patients (seven days after the onset of meningitis), such as papillitis of the optic nerve and arthritis cases.

Extrameningeal manifestations prolong and complicate treatment of meningococcal disease. However they have no significant influence on the outcome of the disease. Out of 42 patients, lethal outcome ensued in two (4.8%) – both from the meningitis group. One of them had pneumonia, while the other thrombophlebitis.

Conclusion

Extrameningeal or systemic manifestations are uncommon complications during the course of both meningococcal meningitis and sepsis. The onset of pneumonia, pericarditis, eye involvement, and arthritis, as well as same rare complications, such as multiple renal embolism with hematuria were observed within the initial seven days of the disease, which indicates that they develop as a direct consequence of meningococcal dissemination. They were more prevalent in the course of meningitis, and they did not influence the disease outcome.

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