[2]*Justyna Janocha-Litwin,* [1,2] *Krzysztof Simon*

RECURRENT MENINGITIS – A REVIEW OF CURRENT LITERATURE

[1.] Department of Infectious Disease, Provincial Hospital in Wrocław
[2.] Department of Infectious Disease and Hepatology, Faculty of Dentistry
Medical University in Wrocław

ABSTRACT

The paper discusses epidemiology, aetiology and the most important predisposing factors associated with recurrent meningitis, as well as the possibilities to prevent this particularly challenging clinical problem. The frequency of recurrent meningitis is estimated to be 2-9%. However, the case fatality is lower compared to a single episode of meningitis. The main causes of recurrent meningitis are considered to be: head injury, congenital or acquired (post-traumatic or post-surgical) cranial or spinal defects, chronic intracranial inflammation, complement system dysfunction, as well as congenital and acquired humoral or cellular immunodeficiency.

Key words: *recurrent meningitis, purulent, nonpurulent,cerebrospinal fluid*

INTRODUCTION

Each case of meningitis in Poland must be obligatorily reported to the National Institute of Public Health - the National Institute of Hygiene (PZH). According to the PZH statistics, in Poland in 2009 number of cases of meningitis and/or encephalitis, which were diagnosed and reported was 2.517. The incidence rate was 6.6 per 100.000 population [1]. Viral aetiology was confirmed in 1.244 cases and microbial aetiology – in 865 cases. Among them in 57% of cases the causative pathogen was identified. In 408 cases other or unknown aetiology was determined.

The statistics on recurrent meningitis are rarely published in Polish literature. However, the review of international publications provides plenty of long-term data. The definition of recurrent bacterial meningitis requires the occurrence of two or more episodes caused by different microorganisms, it can also be the second, and the next episode of abnormalities in the cerebrospinal fluid caused by the same pathogen in interval of 3 weeks after completion of treatment, ie after normalization of CSF following the first episode (2).

ETIOLOGY OF RECURRENT MENINGITIS

The published statistical data on recurrent meningitis is usually based on a long-term clinical observations of a single larger centre. In his review, *M.L.Durand* (3) claims that out of 493 cases of recurrent meningitis treated in 445 patients at the Massachusetts General Hospital between 1962 and 1988, only 9 % (41) of patients actually met the criteria of recurrent meningitis. The authors described 89 episodes in total, in 41 patients. Lower case fatality associated with the recurrence of meningitis compared to the first episode (0% vs. 25%) was observed. It is explained by the increased awareness of early disease symptoms by both the patients and their relatives. As a result, the patients seek medical help much earlier.

Kirsten S. Adriani (4) also emphasizes lower case fastality in cases of recurrent CNS infection (15%) compared to the group of patients with the first episode (34%). In an observational Dutch study conducted on a cohort of patients with bacterial meningitis in 1998-2002, 696 cases of the disease were described; 34 (4.8%) of them met the criteria of recurrent meningitis. In a group of 31 patients, 25 (81%) had two episodes of meningitis, 4 (13%) patients had 3 episodes (in a follow-up period of 3 years). Two single patients experienced 5 and 6 episodes, respectively (3%).

According to this data, recurrent meningitis occurred more frequently in men (74%) versus a single episode of meningitis with comparable incidence for men and women. The more frequent occurrence of recurrent meningitis in men, can be explained by higher frequency of head trauma (e.g. head traffic injuries), which constitutes a risk factor of recurrent CNS infection (53%). Other well established risk factors for the recurrence of meningitis involve craniofacial defects

with the CSF leakage (38%) and immunodeficiency (9%), including HIV infection, status post splenectomy or chronic alcohol abuse. On the other hand, the etiology of recurrent bacterial meningitis is similar to the one identified in a single episode of meningitis. The most common causative pathogens are *Streptococcus pneumoniae* (84%), *Haemophilus influenzae* (8%), Neisseria meningitidis (5%) and *Staphylococcus aureus* (3%).

The study by Joris J. Van Driel et al. [5] is important in understanding the epidemiology of microbial (excluding the infections caused by *Mycobacterium spp.)* and fungal meningitis. The authors analysed 19.163 cases of neuroinfections occuring in 18.915 Dutch patients during 18 years between 1988 and 2005. 202 patients (1.1%) met the criteria of recurrent neuroinfection. In these patients a total number of 450 episodes (2.3%) of meningitis was reported. The criteria of recurrent meningitis, assumed in this study involved: the next episode occurring after 28 or more days following the first episode, or the next episode occurring within less than 28 days, but caused by another pathogen.

Most cases of recurrent meningitis in this group (71%) were caused by the capsule-producing bacteria, such as: *Streptococcus pneumoniae* (40%), *Neisseria meningitidis* (22%) and *Haemophilus influenzae* (9%). Recurrent meningitis occurred more frequently in men (58%) in this study population. Out of 202 patients, 169 (64%) had two episodes of meningitis, 25 patients - three episodes, 5 patients (3%) - four episodes, 2 patients - 5 episodes and a single patient had as many as seven.

When meningitis develops as a result of head trauma, it is referred to as *post-traumatic meninigitis* (PTM). In the survey conducted in 2 US trauma centers between 1992 and 1999 [6], 37 (0.56%) out of 4.788 patients after different head injuries (blunt trauma - 75%, penetrating trauma - 15%) developed neuroinfection. This data complies with the general statistics estimating the risk of PTM development as 0.38-2.03%. The mean time from the injury to the diagnosis of meningitis was 97.7 days. The mortality in post-traumatic meningitis was as high as 15%, which was probably associated with the originally serious condition of the patients due to trauma, and the complication - namely, neuroinfection - could only deteriorate it. The most frequently reported causative pathogens were *S.penumoniae* (in 6 patients), also (but less frequently) *P.aeruginosa* (2), *S.aureus* (1), *E.faecalis* (1), *K.pneumoniae* (1).

The conclusion to the observations mentioned above is that head trauma was the predisposing factor for recurrent meningitis in approximately 28% of patients. The restrospective analysis of 160 patients with CSF leakage following head trauma, carried out by *Eljamel* and *Foy* showed that the highest risk of meningitis (9,1%) occurs within the first week following head injury. The authors estimated the risk of CNS infection development, as a complication of head trauma to be approximately 8% within the first 6 months and 8% per year, later than 6 months after the injury [7].

Fridman (8) observed 51 patients after head trauma with CSF leakage prolonged to over 24 hours. 8 of them (16%) developed meningitis within approximately 6,5 years following the injury. It was noticed that antibiotic prophylaxis used in cases with CSF leakage halved the risk of meningitis. However, the difference was not statistically significant.

Nevertheless, the results of other meta-analyses did not clearly confirm the efficacy of preventive antibiotic therapy in patients with head trauma [9] [10]. *H. Brodie* analysed data of 324 patients from 6 different studies conducted between 1970 and 1995. Antibiotics were used as prophylaxis in 237 patients after head trauma, resulting in CSF leakage. 87 of them did not receive any preventive antibiotic therapy. In patients who received antibiotic prophylaxis, 6 out of 237 developed meningitis (2.5%), and in the group of 87 patients, 9 of them developed meningitis (10%). This difference was statistically significant (p=0.006). On the other hand, the metaanalysis of 12 studies carried out between 1970 and 1996 conducted by *T. Villalobos* [10], involving 1.241 patients after head injury with cranial fractures, showed that the antibiotic prophylaxis (received by 719 patients, and not received by 522), did not prevent development of meningitis in patients with cranial fractures.

After head trauma and CSF leakage, HIV infection is considered the next common risk factor of invasive pneumococcal disease, including pneumococcal meningitis (this infection is observed 46 to 100 times more frequently in this group of patients compared to the general population and the risk increases with the progression of immunodeficiency). HIV infection also predisposes a patient for a criptococcal meningitis or tuberculous meningitis.

Other risk factors, which predispose a patient to recurrent CNS infections are obviously congenital immunodeficiencies, such as complement system dysfunction (deficiencies of complement components), X-linked agammaglobulinaemia, IgG subclass deficiency, common variable immunodeficiency (CVID) and asplenia. According to *Adriani* [4] immunodeficiencies constitute the basis for 9% of recurrent meningitis. In these cases meningitis is usually caused by capsule-producing bacteria.

Other risk factors include CNS defects. Epidermoid and dermoid cysts are enumerated among them, involving both the cranium and the spinal cord, as well as Mondini dysplasia (malformation involving the osseous and membranaceous labyrinth), other malformations of inner ear, meningocele and myelomeningocele.

The factor predisposing to meningitis also include chronic sinusitis, otitis media, mastoiditis, as a result of a direct anatomical communication between the

individual neuro-craniofacial structures. Our own experience appear to confirm this.

The data referred to above, concerns the cases of purulent bacterial CNS infections, whereas the general classification differentiates between purulent vs non-purulent meningitis. Purulent CNS infections are virtually considered to have microbial etiology. The most common causative pathogens in adults include the ones enumerated above. However, they are slightly different in newborns and small children, including: *E.coli* and other Gram-negative bacteria, group B Streptococcus species and *H. influenzae*.

The result analysis of these observations lead to the conclusion that the etiology of purulent recurrent (Table 1) and non-recurrent meningitis is similar; generally *S.pneumoniae* seems to be the most common causative pathogen. More specifically, *N.meningitidis*, and less frequently *S. pneumoniae* causes meningitis in patients with complement system dysfunction (11,12). On the other hand, in patients with penetrating head injuries *S. aureus* is the most common causative pathogen. Eventually, meningitis secondary to Salmonella spp. infection occurs mostly in patients with acquired immunodeficiency, at the stage of AIDS (12).

Table 1. The association between the etiological factor and the established risk factors for bacterial CNS infections. [2]

Etiological factor	Risk factor
Streptococcus pneumoniae	head injury congenital craniopathy meningocele and meningoencephalocele (meningocele/meningoencephalocele) inner ear malformations/ Mondini dysplasia asplenia IgG subclass deficiency complement system dysfunction (C2-C4 deficiency) HIV infection chronic otitis media/ mastoiditis
Neisseria meningitidis	head injury congenital craniopathy meninigocele and meningoencephalocele inner ear malformations/ Mondini dysplasia complement system dysfunction (C2-C9 deficiency)
Haemophilus influenzae	head injury congenital craniopathy inner ear malformations/ Mondini dysplasia chronic otitis media/ mastoiditis
Staphylococcus aureus	meningocele and meningoencephalocele dermoid/ epidermoid cysts head injury
Escherichia coli *Klebsiella* spp. *Proteus* spp.	meningocele (lumbosacral region) dermoid/ epidermoid cysts chronic otitis media/ mastoiditis/ sinusitis
Salmonella spp.	HIV infection

Purulent CNS infections tend to have more rapid course and, if left untreated, may lead to death. The symptoms are typical : fever, malaise, headaches, vomiting, disorders of consciousness and convulsion.

Non-purulent meningitis may have either infective or non-infective etiology. The infective etiological factors contributing to the recurrent CNS infections may include bacteria, rickettsia, spirochaete, fungi, protozoa and viruses. Non-infective meningitis may be drug-induced, a result of an atypical response to NSAIDs; it may also occur during the immune reconstitution syndrome after the commencement of antiretroviral treatment in HIV-infected patients or manifests as a chemical recurrent meningitis, secondarily to the rupture and release of content of intracranial or intraspinal epidermoid or neuroepithelial cysts (14). Generally, the incidence of non-purulent CNS infections is low; their symptoms are less severe, and the course of the disease can be prolonged and occult.

CLASSIFICATION OF RECURRENT NON-PURULENT MENINGITIS by J. Greenlee (15):

1. The progression of chronic CNS infections secondary to tuberculosis, syphilis, borreliosis, brucellosis, fungal infections caused by *Cryptococcus neoformans*, *Coccidioides immitis* may be insidious and gradual, with the episodes of general health deterioration and clinical symptoms of recurrence of meningitis.
2. Recurrent CNS infections secondary to autoimmune/ systemic diseases of unknown etiology, such as sarcoidosis, Sjogren's Syndrome, Behcet's disease and Vogt-Koyanagi-Harada's Syndrome (VKHS). CSF abnormalities concomitant with meningeal signs may also develop in patients with a migraine episode.

A rare although typical example is VKHS, also referred to as uveo-meningeal syndrome, probably an autoimmune disease linked to the cytotoxicity of T cells against melanocytes. Its symptoms involve: alopecia areata, premature graying and uveitis. Neurological symptoms of aseptic meningitis, such as neck stiffness, intracranial nerve damage or tinnitus may also develop. CSF flows at higher pressure, its analysis usually reveals marked pleocytosis (esp. lymphocytosis) as well as elevated protein levels [16].

1. Recurrent CNS infections secondary to periodical reactivation of usually latent HSV infection. Other, rare cases, involve toxoplasmosis, infection caused by Epstein-Barr virus or Candida tropicalis. Between the episodes of meningitis, CSF is usually normal.

D.G. Tender (17) showed that the most common causative pathogen of mild recurrent meningitis is

herpes simplex infection, with HSV 2 predominating over HSV 1. This is also referred to as mild aseptic Mollaret meningitis, which involves recurrent episodes of CNS infections with detectable CSF abnormalities. The episodes are mild and resolve spontaneously; they recur quite frequently - every few weeks or months.

4. Drug-induced aseptic meninigitis (DIAM) - recurrent CNS infections as an atypical response to nonsteroid anti-inflammatory drugs (NSAIDs) or other medications.

In patients with autoimmune diseases, e.g. SLE, connective tissue diseases or systemic vasculitis, the episodes of CNS infection may recur, as a result NSAID use, typically ibuprofen. The episodes of uknown etiology may also be observed in previously healthy subjects, who eventually - within months or years - develop autoimmune disease. In these cases, CSF analysis reveals pleocytosis (esp. elevated count of polymorphonuclear leukocytes) and elevated levels of proteins, which may be suggestive of bacterial etiology. However, glucose level remains normal, which differs this type of meningitis from bacterial one.

Other drugs which are likely to induce meningitis include: rofecoxib, metronidazole, amoxicillin, sulfamethoxazole-trimethoprim, ciprofloxacin, ranitidine, or immunoglobulin G. Therefore it is suggested that in seemingly healthy individuals, diagnosed with drug-induced meningitis, screening for autoimmune diseases be performed (18) In a differential diagnosis of drug-induced meningitis the infective etiology must be excluded, and the temporal relationship between an episode of the disease and drug administration must be determined. The symptoms usually develop within hours (up to months) following drug administration. Drug-induced meningitis is usually rare, its pathomechanism has not been fully explained. Hypersensitivity response type 1 or 3 to a given medication are thought to be involved in the pathomechanism, as well as cross-reactivity to antigens present in the central nervous system (19).

5. Recurrent chemical meningitis caused by the leakage of content of intracranial or intraspinal tumours. The tumours usually invove embryonic cysts, epidermoid or neuroepithelial cysts, teratomas, craniopharyngomas and pituitary abscesses (20). Also, the congenital CNS defects predispose patients to develop secondary infections and bacterial menigitis.

6. Recurrent meningitis during the immune reconstitution syndrome in patients with AIDS, receiving antiretroviral treatment.

Patients with AIDS and the history of treatment for *Crypotococcus neoformans* infection, at the moment of commencement of ARV treatment, potentially during the immune reconstitution syndrome, re-develop neurological symptoms such as fever, memory disturbance or headaches, which symptomatize the recurrence of cryptococcal meningitis. The immune reconstitution syndrome is treated with glicocorticosteroids (21).

The complications of recurrent meningitis are similar to the complications of a single episode. Acute complications include: rapid increase of intracranial pressure, convulsions and septic shock. Chronic complications can manifest as cognitive dysfunction, epilepsy, hearing disorders, damage to other intracranial nerves. Treatment of each meningitis episode involves an attempt to identify the etiology as soon as possible, and to start treatment, initially empirically, with its later adjustment according to the etiological factor.

The second episode of meningitis requires more detailed diagnostic management in order to determine the factors which predispose the patient to recurrence. At this point, diagnosis involves precise neuroimaging such as cranial CT or MRI, spinal imaging can be considered as well as a complete ENT evaluation with audiometry (especially in children), and the assessment of blood derived laboratory markers of immunodeficiency (e.g. complete blood count, IgG subclass assay, level of other immnoglobulins and lymphocyte subtypes) including HIV test.

How can we prevent the recurrence of meningitis? The issue of prophylactic antibiotic use after a head trauma was discussed above. The patients after an episode of bacterial meningitis are advised to consider the vaccines against other common causative pathogens of CNS infections, even including the same etiological factor, e.g. *S. pneumoniae*, since there are many different serotypes of the bacteria. A polyvalent vaccine against *S. pneumoniae, type B H. influenzae* and *N. meningitdis* (A+C+W135+Y) is recommended. The patients with anatomical CNS defects (congenital, posttraumatic or postsurgical) should undergo neurosurgical or ENT reconstructive procedure. This particularly applies to the patients with CSF leakage. Surgical management is also necessary in patients with chemical meningitis, caused by intracranial or intraspinal tumours (obviously depending on tumour location and technical possibilities). Mild meningitis caused by HSV should be treated with the long-term administration of acyclovir (treatment duration has not been specified).

SUMMARY

1. The frequency of recurrent meningitis ranges between 2% and 9%.

2. The mortality in recurrent meningitis is lower compared to a single episode of meningitis.
3. Recurrent episodes of CNS infections occur more frequently in men, which is associated with their higher exposure to potential head trauma - considered to be the main risk factor of recurrent meningitis.
4. Other risk factors for recurrent meningitis include congenital or acquired (post-traumatic or post-surgical) cranial or spinal defects, immunodeficiencies such as complement system dysfunction, congenital humoral or cellular immunodeficiency, and acquired immunodeficiency - also HIV-related.
5. The most common causative pathogen of recurrent menigitis is *Streptococcus pneumoniae*, other common causative pathogens include *N.meningitidis, H.influenza, E.coli, S.areus and Salomnella spp*.
6. Prevention of recurrent meningitis involves the detection of risk factors, the attempt to eliminate them, surgical repair of cranial defects and vaccination against the pathogens known to cause CNS infections (*S.pneumoniae, N. meninigitidis, H.influenzae)*. The use of antibiotics in order to prevent the development of meningitis in patients after head trauma is still debated, and the results are not conclusive.

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Address for correspondence:
Lek med Justyna Janocha-Litwin
I Department of Infectious Disease,
Provincial Hospital in Wrocław
Koszarowa 5 Street, 51-149 Wrocław, Poland
justynajanocha@o2.pl
tel. 71 3261325 w. 242
fax. 71 3255242