



History of development of inflammatory diseases of the nervous system – meningitis and encephalitis

Istorijat razvoja zapaljenjskih bolesti nervnog sistema – meningitis i encefalitis

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Introduction

A look back through history reveals that a man has always been exposed to diseases, injuries and accidents. He has used different ways and methods of treatment, and at the same time investigated the causation of disease outbreaks. Centuries ago, infectious diseases were a great unknown to mankind, primarily due to the inability of early detection of pathogens, but also the attribution of supernatural origin of many diseases of epidemic proportions.

Although described through the history of medicine as a segment of other infectious diseases, most commonly fever or sepsis, with present headache as a symptom, meningitis has long remained unrecognized as a distinct clinical entity. Epidemic forms of meningitis occurrence, history recorded in the beginning of 19th century and the most important discoveries related to inflammation of the central nervous system, meningitis and encephalitis, were published by the end of the 19th century.

History of meningitis evolution

Infections of the central nervous system, which can be of infectious and non-infectious genesis, are inflammatory process of the brain and the brain membranes. These, otherwise serious infections that can endanger human life, take on even greater weight when, not so rare, complicate with neurological manifestations. Bacterial meningitis means inflammation of the meninges, that different types of bacteria cause. Viral meningitis presents a serous inflammation of leptomeninges¹.

First data connected with inflammatory diseases of nervous system were noted by Thomas Willis (1621–1675), English physician, who described patients suffering from "in-

flammation of the meninges and present fever," and it can be said that he spoke of meningitis, even in 1661². The first time the epidemic meningitis was noted in 1805 in Geneva, then 1814 in Grenoble and Genova. After that epidemic appeared in France in 1822 then in 1823 in Germany, and after 7 years at Sunderland³. An epidemic of meningococcal meningitis had been described by Swiss physicians, Gaspard Vieusseux (1746–1814), and Andre Matthey (1778–1842) in Geneva. First epidemic in Africa was described in 1840. They had become more common in the 20th century, so the first bigger epidemic was noted in Nigeria and Ghana (1905–1908), when a large number of people had suffered⁴. The origin of the disease, and even the name of it, stayed unknown. This disease was identified by doctors as "sinking typhoid", or "spotted fever"⁵. Although still Herophilos (335–280 BC), an ancient Greek physician, first explained the anatomical structure of the brain and brain membrane, describing fourth ventricle, representing it as a place of the soul, it was not known for the occurrence of inflammation of the meninges. Herodotus (c.484–425 BC), an ancient Greek physician, spoke of "doctors for the head" in Egypt, who dealt with both physical and mental causes of the disease⁵.

Certainly based on historical medical data, as well as other diseases in prehistoric times, supernatural causes were attributed to the occurrence of inflammatory processes in the brain tissue, also. One particularly popular method of diagnosis, and treatment, linked to brain disease, known in time of prehistory, was a trepanation of the skull or "šaronjanje", name used in some parts of our country as intervention on bone parts of the skull. It was used in the occasion of the existence of neurological diseases, and psychiatric disorders, but most commonly in post-traumatic headaches. While the prehistoric "surgeons", thought that opening the skull can rid

the patient of evil thoughts and demons, the latter in some parts of our country, during the 19th century, the whole process had an element of vendetta. Particularly interesting is the fact that a high percentage of these patients, underwent surgery, and survived without the inflammatory process of the brain and meninges. A staggering figure when one considers that the intervention was performed by opening the skull, with unsterilized instruments, on which occasion would perpetrator watch brain membrane and thus establish "if it is dropped blood to the brain" (Figure 1)^{5,6}.



Fig. 1 – Trepanation – The Extraction of the Stone of Madness (a painting by Hieronymus Bosch).

Nature cause of a disease was first described by Galen (c.130 AD–c.210/c.216AD), a Roman physician and philosopher of Greek origin, who was stating that the challengers were in the water, air and rotting substances, calling them "miasmas". Since the natural cause of the disease was first mentioned in paper "De contagione et contagiosis morbis" by an Italian physician, Girolamo Fracastoro (1478–1553), having started involvement in determining the etiology of the disease and finding cause of the infectious diseases including inflammatory diseases of the nervous system³.

For the occurrence of meningitis various agents have been blamed through the history. Meningitis was commonly called "brain fever" or "brain inflammation" in the past, and it was believed that potential triggers for its appearance were: the sun, the temperature change, mental disorders, stress, and numerous other factors. In the early 20th century, these beliefs were discarded in the United States, as in the most Western European countries. Nerve disturbances and mental disorders, were also blamed, as shown in the literature of Russian writers^{3,7}.

As a very common complication of inflammatory diseases of the nervous system was hydrocephalus, which was represented as an enlargement of brain ventricles due to increased amounts of cerebrospinal fluid in the brain chambers. Hydrocephalus was described by Hippocrates (c. 460–c.370 BC),

Galen and Arabian doctors, who believed it was a disease caused by extracerebral accumulation of water³.

Concept of cerebrospinal fluid (CSF) is closely linked to historical and medical development of meningitis. It is now known that the CSF is fluid that fills the subarachnoid space of the brain and spinal cord, and brain ventricles¹. It is believed that Imhotep, an Egyptian doctor, and the notary, was the author of papyrus from 3000 BC, and the first one who discovered intracranial CSF. Name of cerebrospinal fluid was introduced by Francois Magendie (1783–1855), French physiologist, in the first half of the 19th century. Nicolo Massa (1485–1569), an Italian anatomist, in his book "Liber Introductorius Anatomiae" in 1536 was the first who described the CSF with cerebral chambers, based on autopsies. Previously, it was thought, by the beliefs of Hippocrates and Galen, that the brain ventricles contained "spirit of animals". It is generally accepted in medical history that the CSF was discovered by Domenico Felice Cotugno an Italian physician (1736–1822) (Figure 2). This famous doctor who lived in Naples in the 18th century published a paper, when he was 25, about the anatomical structures of the ear. He stated that not only were brain ventricle but the subarachnoid spaces filled by CSF, which was called "liquor cotunii"^{8,9}.



Fig. 2 – Domenico Cotugno (1736–1822).

A very important moment in the history of development of meningitis, was the introduction of lumbar puncture. Lumbar puncture includes diagnostic procedure used to obtain cerebrospinal fluid, but in rare cases, therapeutic method for reducing increased intracranial pressure¹. In the beginning, the purpose was purely therapeutic. But soon, lumbar puncture was introduced as a diagnostic procedure¹⁰. In 1881 Wernicke performed sterile ventricular puncture and external drainage of cerebrospinal fluid. These were followed-up in 1891 with serial lumbar punctures by Quincke (Figure 3)¹¹.

The first technique was described by an English physician Walter Essex Wynter, in 1889 in patients with tuberculous meningitis, when he used cannulation, which then had more therapeutic than diagnostic significance¹². Definitive lumbar puncture technique was introduced by a German



Fig. 3 – Heinrich Irenaeus Quincke (1842–1922).

physician Heinrich Irenaeus Quincke (1842–1922) who presented his experience at the Conference of Internal Medicine in Wiesbaden, Germany. In the United States, the procedure was implemented in 1891 by Arthur H. Wentworth in the children's hospital¹². Winter's technique was involved in making incisions in 2nd lumbar region, such as major cut and placing a tube with a rubber drainage and so knocked infected content and reduced the pressure¹³ (Figure 4). Also, he measured the level of sugar and protein in the cerebrospinal fluid, describing low sugar in purulent meningitis. He found of the tuberculosis *Mycobacterium tuberculosis* in the CSF and thus diagnosed tuberculous meningitis¹⁴.



Fig. 4 – Lumbar puncture, at the beginning of the 20th century.

Neurotuberculosis is a chronic inflammation of the nervous system, which is primarily caused by *Mycobacterium tuberculosis*, accounting for about 5–10% of all forms of extrapulmonary tuberculosis¹⁵. Tuberculous meningitis was first described by an Edinburgh physician Sir Robert Whytt (1714–1766), but his work was published posthumously in 1768. However, the link between tuberculous bacillus and meningitis was discovered even after 100 years⁴.

In the years after the World War 2nd, at the Clinic of Infectious Disease in Belgrade, a large number of patients with tuberculous meningitis, mostly children, a population that had been the most frequent and the most vulnerable were hospitalized and treated. Great merit in the fight against this disease, which mortality rate was 88.7% during the period from 1947 to 1949 belonged to Professor Dr. Kosta Todorović, a famous infectologist and scientist, who invested great efforts in his work. According to the data from the Clinic of Infectious Diseases, ten years later children were the most numerous patients still, but the mortality rate was 9.5%. The statistics speak in favor of a successful fight of infectology team and associates in post-war years against the serious and deadly disease, and certainly immeasurable satisfaction in recovering patients¹⁶.

In the historical development of meningitis special place had meningeal signs, and the credit for that had scientists Kernig and Brudzinski. Meningeal signs are in fact reflections that occur in response to the increase of elevated intracranial pressure, which can occur when performing certain movements at the examination of patients¹. Disclosed are: stiff neck; sign of Brudzinski that is positive when in passive flexion of the head and neck, the response is flexion of the ankle of hip and knee; the character of the lower Brudzinski is positive, when during flexion of legs in the ankle of hip and knee, due to the stretching of the nerve ischiadic and distal spinal cord, the response is flexion of the other leg in the same joint; a positive sign of Kernig means that in the course of moving the patient from a lying to an upright position, the patient is unable to take a right angle between torso and legs and also when lifting the leg, they can not take the right angle in relation to the body¹.

Vladimir M. Kernig (1840–1917), was a neurologist of Russian-Baltic origin. Kernig's sign was described in 1882 in the article of the Weekly Medical Journal, where was stated that during the years of test cases of meningitis he noticed a sign that had practical value. He stated that "if one attempts to extend the patients knees they will succeed only to an angle of approximately 135°. In cases which the phenomenon is very pronounced the angle may even remain 90° (Figure 5)¹⁷.

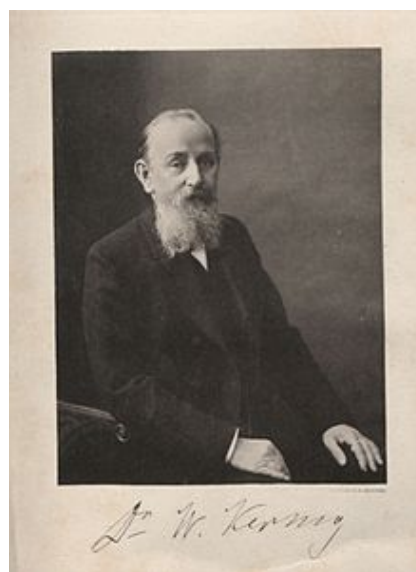


Fig. 5 – Vladimir Kernig (1840–1917).

Jozéf Brudziński (1874–1917) (Figure 6) was a Polish doctor, a pediatrician. After World War I, he renewed the Polish University in Warsaw, and was appointed as a director of the same. In that time, Brudziński released four manu-



Fig. 6 – Jozéf Brudziński (1874–1917).

vers in detection of meningitis. First it was cheek positive sign and that means when putting pressure on both cheeks under zygomatic arch can cause flexion of the forearm and arm. Also, symphyseal positive sign shows that pressure on the pubic symphysis causes flexion of the hip and knee, abduction of the leg. When passive flexion of the knee causes flexion of opposite knee, than it is named Brudziński's reflex. And Brudziński's sign is described as positive, when the passive flexion of the neck causes flexion of the hips and knees¹⁷. The majority of the patients were children, the population most affected by tuberculous meningitis. Brudziński recorded 21 cases of tuberculous meningitis out of 42 investigated cases of meningitis¹⁷.

Contemporary literature registers that bacterial meningitis is caused in 80% of cases mostly by *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*¹. These organisms that caused meningitis were discovered in the late 19th century. Serum therapy against meningococcal meningitis was introduced by a physician George Joachmann (1874–1915) in Germany and Simon Flexner (1863–1946) in America. Antibiotic therapy began in the 20th century with the use of sulfonamides by Francois Schwentker (1904–1954) and penicillin by Chester Keefer (1897–1972), an American physician. The vaccination began in early 20th century¹⁸.

In 1881, two microbiologists, George M. Stenberg (1898–1915) in the United States, and Louis Pasteur (1822–1895) in France, independently described a couple of bacteria in human saliva. Both of them found *diplococcus* in the blood of rabbits. Pasteur called it „Microbe septicémique du saliva“, and Stenberg „*Micrococcus pasteurii*“. In 1886 it was named *Pneumococcus* by Frenkel, due to the possibility to cause pneumonia¹⁹. However, the full name of *Streptococcus pneumoniae* was obtained in 1974 according to the growth of bacteria in chains. The role of germs in lobar pneumonia was proven in 80's of the 19th

century and later in the same decade, *pneumococcus* was presented as the cause of meningitis and middle ear infections¹⁹.

An Austrian pathologist and bacteriologist Anton Weichselbaum (1845–1920) in 1887 was the first who showed that there was a connection between *N. meningitidis* (then known as *Diplococcus intracellularis meningitidis*) and epidemic cerebrospinal meningitis. An Italian scientist, Vieusseux (1779–1863), was the first who described meningococcal disease, in Geneva 1805 and he was stating that the infection was being spread through "bad air". Simon Flexner succeeded in producing meningococcal serum in 1906 of equine origin, which reduced mortality of meningococcal disease from 75%–80% to 30%. The disease was fatal to the military forces during World War II, but thanks to the antiserum and antimicrobial treatment has become a curable disease. One of the biggest epidemic of meningococcal meningitis in the history of medicine, was in Brazil in 1974 before a vaccine was used. The World Health Organization annually records at least 500 000 new cases of meningococcal disease, resulting in more than 50 000 deaths annually²⁰.

Haemophilus influenzae was described in 1892 by Richard Pfeiffer, during an influenza pandemic, and for a long time, until 1933 was considered as a challenger of influenza, so the infection by this bacteria was often referred as "bacterial flu". Later was discovered that it caused bacteremia, pneumonia and acute bacterial meningitis in infants and children. From 1990 a conjugated Hib vaccine that reduces the incidence of meningitis has been used in the United States²¹.

In the prevention of bacterial meningitis at the present time, in addition to maintaining a healthy life style and sanitary habits, avoiding close contact with carriers of a disease, chemoprophylaxis and immunoprophylaxis are used. Rifampicin, ceftriaxone and ciprofloxacin are suggested in case of meningococcal disease. Immunoprophylaxis covers a monovalent vaccine antigen of specific meningococcal serogroup and quadrivalent, and does not offer protection against the B serogroup. Chemoprophylaxis of pneumococcal infections is being implemented in the form of rifampicin, and immunoprophylaxis includes 23-valent pneumococcal vaccine. *Haemophilus influenzae* B meningitis includes rifampicin chemoprophylaxis and immunoprophylaxis implementation of conjugated vaccines with polyribose-ribitol phosphate *Haemophilus influenzae* B with the carrier protein. Also hyperimmune globulin can be used according to indications^{1,22}. Before using specific antisera, the odds of one who suffered from bacterial meningitis were bad. In 1920 a total of 77 of the 78 children at Boston Children's Hospital with *Haemophilus influenzae* meningitis died. A similar was the prognosis for untreated pneumococcal meningitis when from 300 observed patients all died. Meningococcal meningitis in the beginning of the 20th century had a mortality rate of 75–80%. Simon Flexner succeeded in use of intrathecal equine meningococcal antiserum in 1,300 patients in 1913, when he reduced mortality to 31%. Unfortunately, forecasts with pneumococcal meningitis stayed bad and after using specific antiserum. In the thirties of the last century, mortality rate in meningococcal meningitis decreased introducing sulfonamides. In the early 50's of the last century, the use of chloramphenicol and

sulfadiazine reduced the number of fatal cases, and thus ruled out the use of antiserum. Penicillin therapy of pneumococcal meningitis began in the mid-40's of the last century. In the second half of the 20th century, in the treatment of bacterial meningitis were used: intravenous penicillin, ampicillin and cephalosporins of 3rd generation¹⁸. It is important to begin empirical treatment, and than to identify the causative agent and use the target – specific therapy. Penicillin, chloramphenicol and ampicillin, ceftriaxone, amikacin, meropenem, ciprofloxacin, cephalosporins of the 4th generation parenterally are used^{1,22}. In patients with *Haemophilus* meningitis dexamethasone was introduced in 1990 too, which has not changed mortality, but reduced the existence of neurological sequelae, especially hearing loss. A particular problem in the antibiotics era makes the emergence of antimicrobial resistance. In future, more emphasis will be placed on preventive, rather than therapeutic measures^{1,22}.

Complications of bacterial meningitis may be systemic, related to distant organs or neurological nature. Although much less common, neurological complications can be very serious. The most common neurological complications include: hearing loss, motor deficits, cognitive defects and problems with speech, sensory deafness, followed by seizures and motor deficit, which is more common in children. Patients with bacterial meningitis are admitted to the intensive care unit if they are in a coma or with complications of the disease. Very common, serious and complex complications are reported during viral encephalitis, due to the possibility of being threatened as emergencies. Neurological sequelae are related to nerve damage, seizures, hemiparesis, as well as damage of intelligence¹.

History of viral meningitis and encephalitis

It is known, today, that the causes of acute viral meningitis make a wide range of viruses among which the most common are: enteroviruses, mumps virus, arboviruses, lymphocytic choriomeningitis virus (LCM), and herpes viruses (HSV)²³. Acute viral encephalitis is difficult infectious disease with abrupt beginning, progredient flow and carries a high risk of complications. It presents the inflammation of the brain parenchyma that occurs due to direct cytopathic effect of the virus or during viremia²³. Although almost all of the viruses can cause encephalitis, usually a tropism in brain tissue expresses herpes viruses, influenza viruses, smallpox viruses and Human immunodeficiency virus (HIV), and also rabies, arbo and adenoviruses²⁴.

In the past, it was not known very much about encephalitis, and the clinical picture was described mainly as a severe form of meningitis. Virchow Rudolf, a German scientist and pathologist described encephalitis in his work³. Aulus Cornelius Celsus (c. 25 BC–c. 50 AD), a scientist and doctor, was the first who described ear disease, and three kinds of "madness" of which one was called encephalitis "letargos", during which he proposed binding people who have seizures³. Since Dmitry Ivanovsky (1864–1920), a Russian virologist, in 1892 in his article described non-bacterial causes of tobacco mosaic disease, which infects tobacco plants passing

through a porcelain filter, as well as the discovery by Martinus Beijerinck's (1851–1931), a Dutch microbiologist, who in 1898 repeated experiment of Ivanovsky and discovered the infectious agent who called virus, until today more than 5,000 species of virus have been described, but there are millions of different types Sve pobrkano ne mogu da znam sta je trebalo reci. With regard that encephalitis can cause any virus, the historical development of encephalitis is directly related to the discovery of the virus that has been found to cause it²⁵. The first discovered viral agent in humans was virus of yellow fever in 1901 discovered by Walter Reed. It was followed by discovery of Rabies virus (Remlinger, Riffat-Baz) and in 1906 smallpox viruses. Then polio virus, chicken leukemia virus were discovered in 1908, as well as in 1911 Rous sarcoma virus. Swine flu was revealed in 1931, and human influenza virus in 1933. There are a number of undiscovered species of human viruses. More than two-thirds of the human viruses can infect human hosts, first mammals, sometimes birds. But not all newly discovered viruses are new because many of them have been present in humans for a long time, but they have been found soon²⁶.

Discovery of encephalitis contracted through ticks (arboviral encephalitis) occurred in the Far East in 1937 and the first vaccine was discovered a year later²⁷. St. Louis encephalitis was noted in 1933, and within 5 weeks in the fall of the epidemic of encephalitis in St. Louis, the Missouri, over 1,000 cases were reported. The virus was isolated in monkeys and white mice. Japanese encephalitis had origin in 1500's in Indonesia, the Malaysia region, but in the thirties of the last century was revealed as forms of arboviral encephalitis. From 1950 to 1970 a great interest was shown in the "slow viral infections", considering them as a potential model for chronic diseases of the nervous system. Owing to diagnostic methods and advances in molecular medicine, modern era of neurovirology has begun. Lately, new viruses have been detected: Nipah, HIV, West Nile, which influence the occurrence of encephalitis²⁵.

The infections caused by Nipah virus were noted as illness of pigs and humans during September 1998 to April 1999 which resulted in death of 105 people. The dominant clinical syndrome in people was encephalitis, which often ended with coma during 48 h. Nipah virus was firstly characterized as a cause of Japanese encephalitis, but later was determined that the cause was a virus of the *Paramyxoviridae* family. Friut bats were pronounced as the primary natural reservoir of the virus²⁸.

West Nile virus was isolated in 1937 from febrile patients in areas of West Nile in North Uganda. During the observation of clinical picture, the neurotrophic effect of the virus was discovered. The first outbreak occurred in Israel in 1951 during which the majority of the diseased were children. Through the outbreaks in Egypt, the manner of transmission by vectors was found. Than the outbreak appeared in an urban environment in 1996 by vectors in Romania, followed by Italy, Israel, and as meningoencephalitis in 1999 in Russia and New York City. From then, the occurrence of epidemic and sporadic cases, with clinical manifestations of encephalitis was recorded²⁹. Human immunodeficiency vi-

rus (HIV) was detected for the first time in 1981 in the United States, primarily among addicts of psychoactive substances and homosexuals, who had symptoms of pneumonia with *Pseudocystis carinii*. In 1983 Robert Gallo and Luc Montagnier claimed independently one of another, that new retrovirus was cause of acquired immunodeficiency syndrome (AIDS) in patients and published their observations calling them Human T-lymphotropic viruses (HTLV), and Lymphadenopathy virus – associated (LAV). In 1986 both viruses were called HIV³⁰.

Limbic encephalitis was mentioned in 1968 for the first time. It was associated with cancer, in context of paraneoplastic syndrome. Today, one can specify a viral origin of the disease, autoantibodies mediated encephalitis and encephalitis as part of an autoimmune disease³¹.

Herpes simplex virus (HSV) is responsible for 5–10% of cases of encephalitis around the world, and this virus as a trigger of encephalitis has been given special attention¹. HSV infections have been known since ancient Greece. Hippocrates described the spread of HSV lesions, calling them herpes. Even Shakespeare described it in his works. But in 1893 Vidal recognized human transmission of HSV infection from person to person, and in 1919 Lowenstein confirmed experimentally the infectious nature of HSV. During the 1920's and 1930's the nature of diseases such as meningitis challengers were discovered. During 40's and 50's was found that virus caused other diseases. *Vari-cella zoster* virus had had a long history, and it took a long time to be separated from other kinds of smallpox virus. Epstein-Barr virus was isolated as a viral particle from limfoblastoid cells from Burkitt lymphoma. *Cytomegalovirus* has been detected recently, found in patients with citomegalovirus inclusion disease. In 1888 the same origin of these viruses was proposed³².

Through the history of medicine, it has been excelled a special relationship between influenza virus with pandemic proportions and appearance of encephalitis as a complication of primary infection. In 1933 English doctors isolated the influenza virus type A, while in 1940 and in 1950 type B and type C virus were isolated. Outbreaks of flu were recorded in Europe as early as 1510 and in 1557. In 1580 the flu was expanding in Africa and Asia, reported as the first known pandemic flu. Thereafter, three pandemics during the 18th century were noted, as well as three pandemics during 19th century. During the 20th century, they were noted in 1918 "Spanish fever", in 1957 "Asian flu" and in 1968 "Hong Kong flu". At the end of the World War I "Spanish flu" was one of the deadliest pandemics in history of mankind, which claimed about 50 million people, in fact 5 times more lives than the World War I³³. Many people who recovered from influenza, felt for a long term consequences, which appeared

many years after epidemic. Phenomenon was described by dr Aleksandar Radosavljevic: "one of the main symptoms was a lethargic condition with a numb facial expression, so that the face of the diseased had the expression of a statue or a mask. The disease was called "encephalitis lethargica"³⁴. Vladimir F. Vujić (1894–1953), a famous neurologist and psychiatrist, described the new phenomenon for Kaligaris syndrome, a particular kind of disease of the brain and also meningeal sign, later named "Sign of Vujić". In the 1939 Vujić was collaborating with a physician Kurt Levy, and formulated entity of encephalitis larvata in a book "Die Patologie des optischen Nachbilder". He studied and analyzed the flu epidemic in Belgrade in 1948 and published a monography "Encephalitis larvata"³⁵.

Current treatment of viral meningitis rarely involves administration of antiviral therapy and treatment is based on symptomatic and substitution therapy and rest. Anti-edematous treatment is required in severe cases^{1, 24}. In addition to hygiene and sanitation measures and protection from respiratory infections, as well as insects and veterinary measures, immunization is very important, also. The immunization is now conducted in order to prevent poliomyelitis, mumps and arbo-virus infection in endemic areas, and immunization against flu is important. First vaccines were produced in 1941. It was important to prevent the mass spread of flu among soldiers during the World War II. Passive immunoprophylaxis is conducted using hyperimmune immunoglobulin^{1, 36}. Severity flow of encephalitis requires constant monitoring of vital functions in intensive care units. It is compulsory to perform antiedematous therapy. It is very important to use an antiviral treatment, corticosteroids, proton pump blockers, sedatives, and antibiotics, if necessary. In addition to basic hygienic and sanitation measures, prevention of encephalitis is reflected in active immunization against possible pathogens. Immunoglobulins may also be used in cases of immunodeficiency^{1, 37}.

Conclusion

Although unrecognized as an inflammatory process of the nervous system in the past, meningitis and encephalitis, by their difficult course, uncertain outcome, complications, and possibility of epidemic occurrence left a big mark on the history of medicine. Today, owing to implementation of an adequate therapy these diseases have a better prognosis. But the story does not end here, because there must always be a willingness to discover new potential causes of meningitis and encephalitis, and therefore a timely response.

R E F E R E N C E S

- Begovac J, Božinović D, Lisić M, Baršić B, Schonwald C. Infectology. Zagreb: Profil International; 2006. (Croatian)
- Tyler KL. Chapter 28: a history of bacterial meningitis. *Handb Clin Neurol* 2010; 95: 417–33.
- Stanojević V. History of medicine. Beograd-Zagreb: Medicinska knjiga; 1953. (Serbian)
- Mandal A. History of meningitis. News-Medical net. 2012. [cited 2015 Dec 15]. Available from: <http://www.news-medical.net/health/History-of-Meningitis.aspx>
- Glesinger L. Medicine through Centuries. Zagreb: Zora; 1954. (Croatian)
- Dimitić B. Testimonies about trepanation in the nation. In: Dimitić B, editor. History of medicine. Project Rastko. Rastko. Net. 2008. [cited 2015 Dec 15]. Available from: <http://www.rastko.rs/rastko/delo/12052>
- Zagazdin Y. Meningitis, a whirlpool of death: Literary reflections and Russian cultural beliefs. *Prog Brain Res* 2013; 206: 35–58.
- Herbowski L. The Maze of the Cerebrospinal Fluid Discovery. *Anat Res Int* 2013; 2013(8): 596027.
- Di Leva A, Yaşargil GM. Liquor cotunnii: The history of cerebrospinal fluid in Domenico Cotugno's work. *Neurosurgery* 2008; 63(2): 352–8.
- Frederiks JA, Koehler PJ. The first lumbar puncture. *J Hist Neurosci* 1997; 6(2): 147–53.
- Aschoff A, Kremer P, Hashemi B, Kunze S. The scientific history of hydrocephalus and its treatment. *Neurosurg Rev* 1999; 22(2–3): 67–93; discussion 94–5.
- Lumbar puncture. Wikipedia, the free encyclopedia. [last modified 2015 December 6]. Available from: https://en.wikipedia.org/w/index.php?title=Lumbar_puncture
- Pearve JM. Walter Essex Wynter, Quincke, and lumbar puncture. *J Neurol Neurosurg Psychiatry* 1994; 57(2): 179.
- Biography of Heinrich Irenaeus Quincke. Whonamedit - dictionary of medical eponyms. [cited 2015 Dec 15]. Available from: www.whonamedit.com/doctor.cfm/504.html
- Garg RK. Tuberculosis of the central nervous system. *Postgrad Med J* 1999; 75(881): 133–40.
- Todorović K. Acute infectious disease. Textbook for students of medicine. Beograd-Zagreb: Medicinska knjiga; 1981. (Serbian)
- Ward MA, Greenwood TM, Kumar DR, Mazza JJ, Yale SH. Josef Brudzinski and Vladimir Mikhailovich Kernig: Signs for diagnosing meningitis. *Clin Med Res* 2010; 8(1): 13–7.
- Swartz MN. Bacterial meningitis: A view of the past 90 years. *N Engl J Med* 2004; 351(18): 1826–8.
- Watson DA, Musber DM, Jacobson JW, Verhoef J. A brief history of the pneumococcus in biomedical research: A panoply of scientific discovery. *Clin Infect Dis* 1993; 17(5): 913–24.
- de Souza AL, Seguro AC. Two centuries of meningococcal infection: From Vieusseux to the cellular and molecular basis of disease. *J Med Microbiol* 2008; 57(Pt 11): 1313–21.
- Schubert A, Messonnier NR. From pandemic suspect to the postvaccine era: the Haemophilus influenzae story. *Clin Infect Dis* 2007; 44(6): 817–9.
- Lieberman JM, Greenberg DP, Ward JJ. Prevention of bacterial meningitis. Vaccines and chemoprophylaxis. *Infect Dis Clin North Am* 1990; 4(4): 703–29.
- Koskineniemi M, Rantalaaho T, Pääparinen H, von Bonsdorff CH, Färkkilä M, Järvinen A, et al. Infections of the central nervous system of suspected viral origin: a collaborative study from Finland. *J Neurovirol* 2001; 7(5): 400–8.
- Romero JR, Newland JG. Viral meningitis and encephalitis: Traditional and emerging viral agents. *Semin Pediatr Infect Dis* 2003; 14(2): 72–82.
- Booss J, Tselis AC. A history of viral infections of the central nervous system: foundations, milestones, and patterns. *Handb Clin Neurol* 2014; 123: 3–44.
- Woolhouse M, Scott F, Hudson Z, Hone R, Chase-Topping M. Human viruses: discovery and emergence. *Philos Trans R Soc Lond B Biol Sci* 2012; 367(1604): 2864–71.
- Pogodina VV. The 70th anniversary of discovery of tick-borne encephalitis. A path to true history. *Vopr Virusol* 2007; 52(5): 5–8. (Russian)
- Field H, Young P, Yob JM, Mills J, Hall L, Mackenzie J. The natural history of Hendra and Nipah viruses. *Microbes Infect* 2001; 3(4): 307–14.
- Sejvar JJ. West Nile virus: An historical overview. *Ochsner J* 2003; 5(3): 6–10.
- History of HIV/AIDS. Wikipedia, the free encyclopedia. [cited 2015 Dec 15]. Available from: https://en.wikipedia.org/wiki/History_of_HIV/AIDS
- Yuasa T, Fujita K. Limbic encephalitis: History, symptoms, and the latest classification. *Brain Nerve* 2010; 62(8): 817–26. (Japanese)
- Historical Background: Human Virology at Stanford [cited 2015 Dec 15]. Available from: <https://virus.stanford.edu/herpes/History.html>
- Influenza. Wikipedia, the free encyclopedia, last modified on 25 January. [cited 2016 Jan 26]. Available from: <https://en.wikipedia.org/wiki/Influenza>
- Radusin M. The Spanish flu: Part II: The second and third wave. *Vojnosanit Pregl* 2012; 69(10): 917–27.
- Pantović M, Milovanović S, Milovanović D, Pantović V, Matović M, Ravančić B, et al. Cornerstones of Serbian medicine: Dr. Vladimir Vujić. *Serb J Exp Clin Res* 2009; 10(1): 5–9.
- Venkatesan A, Geocadin RG. Diagnosis and management of acute encephalitis: A practical approach. *Neurol Clin Pract* 2014; 4(3): 206–15.
- Rozenberg F, Deback C, Agut H. Herpes simplex encephalitis: From virus to therapy. *Infect Disord Drug Targets* 2011; 11(3): 235–50.

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