Neurological symptoms in infectious diseases

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Abstract

Introduction: In the course of infectious diseases, various neurological symptoms can be observed.

The aim of the study: The article focuses on the neurological symptoms presented in infectious diseases.

Material and method: Standard criteria were used to review the literature data. The search of articles in the PubMed, Google Scholar, ReaserchGate database was carried out using the following keywords: neurological symptoms, infectious diseases, neuropathology.

Description: Infectious diseases such as Lyme diseases, syphilis, group A beta-hemolytic Streptoccocus infection, rabies, tetanus, botulism, poliomyelitis, AIDS can be manifested by neurological symptoms. Symptoms that appear as a result of the development of the diseases include these simple, non-specific symptoms such as weakness, abdominal pain, fever or headache to more serious, life-threatening as respiratory failure, arrhythmias.

Summary: Many infectious diseases can cause neurological symptoms. It is important to remember about the possibility of these diseases during the diagnostics of neurological conditions.

Keywords: neurological symptoms, infectious diseases, neuropathology

INTRODUCTION

In the course of infectious diseases, various neurological symptoms resulting from damage to both the central nervous system (CNS) and peripheral nervous system can be observed. Usually, nervous system involvement is a secondary complication of a systemic infection, and the symptoms of neurological disorders appear in advanced stages of the disease [1]. In addition, the involvement of the nervous system is usually associated with a more severe course and worse prognosis. However, in some infectious diseases, the etiological factor exhibits neurotropic activity and occupies nervous tissue relatively early. Regardless of the time from infection to involvement of the nervous system, this condition significantly affects the quality of life and mortality in this group of patients. Fast diagnosis of the underlying pathology is the key to appropriate treatment so early and aggressive treatment becomes a chance to improve the patient's neurological condition without any permanent complications.

The article focuses on common infectious diseases that can cause neurological symptoms. To this end, scientific publications in the following databases have been reviewed: Pubmed, Google Scholar, ReaserchGate. Typical symptoms of nervous system involvement in specific infectious diseases have been described.

RABIES

Rabies is an acute infectious disease with an extremely dynamic course and high mortality [2]. The etiological factor of the disease is *Rabies virus (RABV)* of the genus *Lyssavirus* and the *Rhabdoviridae* family, which has neurotropic properties. Seven RABV genotypes have been identified. Genotype 1 (classic rabies virus) is the most widespread genotype in the world. Laboratory strains used for vaccine production belong to this group [3]. Genotypes 2 (*Lagos bat virus, LBV*), 3 (*Mokola virus, MOKV*) and 4 (D*uvenhage virus, DUVV*) are found on the African continent, genotypes 5 (Eur*opean bat lyssavirus 1, EBLV-1*) and 6 (*European bat lyssavirus 2, EBLV-2*) in Europe, while the genotype 7 virus (*Austrialian bat lyssavirus, ABLV*) in Australia [4].

Rabies is a zoonosis, and the reservoir of the genotype 1 virus is canine, including dogs, foxes, wolves and wild carnivores e.g. bats and raccoons [4]. Infection with rabies virus usually occurs as a result of bite or contact of damaged skin with saliva of infect animal. As a result of being bitten by a infected animal, virus contained in salivary enters skeletal muscle cells. This is where the virus replicates, which lasts from a few to several hours [5]. Then virus binds to the nicotinic receptor for acetylcholine in the postsynaptic membrane of the neuromuscular plate and moves to the axon. As a result of retrograde transport, *RABV* moves through the peripheral nerve fibers and reaches the spinal cord. In gray substance of a brain replicates again, after which it spreads to other organs with autonomic efferent fibers [5].

By the fact that the virus mainly occupies the nervous tissue, it contributes to significant dysfunction of neurons [6]. There are two clinical forms of rabies in humans: excitatory and paralytic [7]. There are also cases when the excitatory type becomes paralytic form. In both forms of the disease, the initial symptoms are non-specific; lack of appetite, fever, headache, nausea, vomiting, diarrhea, constipation, as well as itching, burning and sensation in the area of the bite. After 2 to 4 days, the complete clinical picture of the disease develops. Symptoms of excessive psychomotor agitation, nervousness, anxiety, visual and auditory hallucinations, confusion, as well as drooling, painful muscle spasms, hydrophobia, aerophobia, dysphagia, difficulty breathing, and finally convulsive seizures and focal paresthesia appear [8]. After the excitatory period, apathy, paralysis and coma appear [9]. After appearance of rabies symptoms this disease becomes incurable. It comes from the fact that the rabies virus is present in the CNS (and causes anterior horn cell dysfunction) long before the onset of clinical symptoms [10]. Death occurs as a result of suffocation.

Thanks to the introduction of numerous rabies prevention programs this disease is rare in the European population nowadays [11]. However, rabies, because of its high mortality, should be included in the differential diagnosis of acute encephalitis and unexplained etiology.

POLIOMYELITIS

Poliomyelitis (also known as infatile paralysis or Heine-Medin's Disease) is a viral infection caused by the *Poliovirus* [12]. The source of infection is the sick or carrier, and the infection occurs through the faecal-oral route. The incubation period lasts on average from 9 to 12 days [13]. *Polioviruses*, after entering the body, multiply in the intestines, and then enter the blood, which carries them to other parts of the body, including the CNS. The disease can occur in one of two clinical forms of the disease - polio nonparalytic or paralytic [14].

In most cases (90–95%), the disease occurs in nonparalytic form, which can occur in 3 different forms:

1. subclinical (72%);

2. abortive poliomyelitis (24%) - there are non-specific symptoms lasting several days (such as gastrointestinal complaints, malaise, fever);

3. aseptic meningitis (4%) - initially there are similar symptoms as in the abortive poliomyelitis, however, after about 2 days appear stiffness and pain in the neck, spine and lower limbs as well as headache and vomiting [15]. Symptoms last 2-10 days, after which usually disappear spontaneously and leave no complications.

Paralytic polio is much less common, it affects 1-2% of all patients [16]. Prodromal symptoms resemble the clinical picture of abortive poliomyelitis, then the disease goes into an asymptomatic period of several days. After this time, a full clinical picture of the disease appears, because usually at this stage of the disease massive involvement of motor neurons within the anterior horns of the spinal cord and motor cortex already occurs [16]. The paralytic polio can occur in two forms:

1. spinal polio - occurs in most cases of paralytic polio, manifests as asymmetrical flaccid paralysis of the lower limb, less often the upper limbs, with the suppression or weakening of reflexes, however, usually superficial and deep sensation is maintained in patients, therefore in cases of loss of sensation can be initially rule out polio virus infection [14];

2. bulbar polio - it constitutes about 2% of paralytic polio, it consists in damage to vegetative centers, therefore it is a direct danger to life [17].

Mortality in the course of paralytic polio is 2-5% in children and 15-30% in adults. Death in the course of paralytic polio virus infection occurs as a result of respiratory muscle involvement [18].

In some patients (20-30%) after polio, after about 25-30 years of stabilization of the neurological state, new symptoms of peripheral motor neuron damage appear. This condition is called Post-Polio Syndrome (PPS) [19]. In PPS, a triad of characteristic symptoms is: 1. progressive muscle weakness; 2. pathological fatigue; 3. muscle and joint pain [20]. Less common symptoms include: reduced pain and cold tolerance, sleep disturbances, muscular atrophy, respiratory and swallowing disorders [21].

Currently, as a result of the Global Polio Eradication Initiative (GPEI), which began in 1988, the incidence has been reduced by 99% [22]. Despite this, new cases are constantly registered, which delays reaching the state of full eradication of the disease in the world [23].

AIDS

AIDS is a disease affecting many systems. Among them is also the nervous system, whose infection is considered in two forms. The first of these is disorders associated with the primary HIV infection, while the second is associated with the occurrence in patients of opportunistic diseases that cause neurological symptoms. These are, among others tuberculosis, cryptococcosis or syphilis. Disorders associated with primary HIV infection include neurocognitive disorders (HIV-Associated Neurocognitive Disorder, HAND), peripheral neuropathies, myopathies, and myelopathy [24]. HAND can be divided according to the Frascati Criteria into: 1. Asymptomatic Neurocognitive Impairment (ANI); 2. Mild Neurocognitive Disorder (MND); 3. HIV-Associated Dementia (HAD) [25]. Cognitive disorders associated with HIV have a slow onset that can manifest themselves through attention deficit disorder, memory disorders, and executive functions. They are caused by many processes caused by both the virus and the host. These include the processes of nerve damage by macrophages and cytokines, as well as damage resulting from opportunistic infections [26]. A study by Hellmuth et al. showed that neurocognitive disorders affect about 33% of participants with acute HIV infection. In addition, it was also shown that 34% of patients with neurological symptoms experience a slowdown in hand and finger movements caused by neuropathy [27]. However, a study in India showed, that the most common neurological symptom of HIV infection is headache (72%), more than half of the patients also had sensory disturbances (57%), some patients also complained of tingling and numbness (30%) [28, 29]. In patients infected with the virus, we can also observe symptoms of delirium, the most common

of which is delirium accompanied by cognitive impairment, apathy or dysphoria [30]. In addition, patients may have symptoms such as manic symptoms, psychosis or anxiety [31, 32, 33].

NEUROBORRELIOSIS

Neurological complications of Lyme Disease is most often caused by *Borrelia garinii* (72%), and much less often by *Borrelia afzelii* (28%) or *Borrelia burgdorferi sensu stricto* [34, 35]. The incidence of Neuroborreliosis (NB) is estimated at around 40% of Lyme Disease cases.

The nervous system may be damaged in the course of many reactions dictated by the predisposition of the bacterium itself, such as direct spirochetes invasion and the toxic-metabolic inflammatory processes generated by this infection [36, 37].

Depending on the duration of the disease, neuroborreliosis is divided into early NB when the symptoms of the disease persist for up to 6 months, and late NB when the symptoms occur more than 6 months after infection [38]. In early stadium, neuroborreliosis includes: 1. cranial nerve paralysis; 2. lymphocytic meningitis and / or brain inflammation, and 3. radiculopathies and peripheral neuropathies [39, 40].

Cranial nerve paralysis affects 5% of Lyme Disease sufferers. It can be unilateral or bilateral and most often affects the facial nerve. It usually disappears after a few weeks of treatment. Lymphocytic meningitis is often mild and its only symptomatic may be a headache. It is found in about 2% of children with Lyme Disease and often coexists with facial nerve paralysis [41]. The interaction of meningitis, cranial nerve paralysis and nerve root disorders is called Garin-Bujadoux-Bannwarth syndrome which is pathognomic for neuroborreliosis [42].

The multiple symptomes of the disease results from not only the duration of the infection, but also from the diversity of bacterial locations. Note that patients with neuroborreliosis with the blood disorders observed in the SPECT images correlate with the cognitive disorders, changes in blood flow in the occipital area of the brain can cause the vision disorders [43]. Equally frequent places of bacterial existence are the hypothalamus, which leads to thermoregulation disorders [44]. Patients will embrace cold and shivers. In addition to neurological symptoms, psychiatric disorders may appear, which usually occur after a longer duration of infection. These include anxiety disorders and affective disorders [44, 45].

Late neuroborreliosis occurs in the form of a progressive encephalitis manifested as spastic paralysis, sphincter paralysis, cranial nerve paralysis, cognitive disorders, dementia or psychotic syndromes [46, 47]. In neuroimaging studies of late neuroborreliosis, changes are

similar to those in Multiple Sclerosis, which often makes it difficult to distinguish between the two diseases [48].

The multiple symptoms of Lyme disease poses many diagnostic difficulties for doctors, and it should be remembered that untreated or incorrectly treated Lyme disease significantly worsens the patient's standard of living [49].

TETANUS

Tetanus is another disease that manifests itself as a neurological disorder. It is an infectious disease, but its direct cause is not the bacterium that is multiplying in the body, but the toxin it produces - tetanospazmin [50]. *Clostridium tetani* Gram-positive, anaerobic, rod-shaped bacteria occurring in the ground and producing round spores is the factor responsible for this disease. Interestingly, other mammals can also be sick for tetanus, including farm animals, but birds are resistant. Tetanus is called a wound infection because bacterial growth occurs in previously wounded skin. After penetrating the damaged skin, spores develop, which is supported by anaerobic conditions in deep wounds. The multiplying bacteria produce toxins: tetanospazmin, tetanololysin and fibrinolysin [50].

Tetanospazmin is a neurotoxin that attacks nerve cells. The toxin released by the bacteria binds to GD1b and GT1b gangliosides on the membranes of local nerve endings, then penetrates into the axon from where it is transported back to the cell body [51]. First, motor and then sensory and autonomic system neurons are affected [52]. Symptoms occur when the toxin reaches the spinal inhibitory interneurones. Further transport means that it appears in the brain stem and midbrain neurons. The direct cause of the appearance of symptoms is blocking the release of neurotransmitter inhibitors: glycine and gamma-aminobutyric acid, which blocks the physiological neuronal inhibition processes and leads to permanent excessive stimulation of motor neurons.

The tetanus is characterized by a triad of symptoms: muscle stiffness, muscle spasm and if a severe systemic form develops - autonomic disorder. Initial symptoms are usually neck stiffness, sore throat and problems with mouth opening [53]. The masseter muscle contraction causes jaws, and the facial muscle contraction causes a characteristic grimace - called risus sardonicus - a sardonic smile. Stiffness of the neck muscles leads to head retraction and, together with the stiffness of the torso, can lead to the development of opisthotonus [53]. There are also difficulties in breathing due to a decrease in the compliance of the chest wall, in addition there is a progressive contraction of the pharynx and larynx muscle leading to obstruction of the respiratory tract and respiratory failure. In addition to increased muscle tone, episodic

muscle cramps occur. These contractions may look like episodes of seizures and are strong enough to lead to fractures, tendon damage and even rupture [54]. There are symptoms from the autonomic system.

Increased sympathetic tension causes persistent tachycardia and hypertension. Distinct vasoconstriction and fever are seen and there is an increase in plasma catecholamine concentration. Severe hypertension and tachycardia may alternate with deep hypotension, bradycardia, which may result in cardiac arrest [55, 56]. Other signs of increased sympathetic activity include abundant salivation and increased bronchial mucus secretion, gastric obstruction, intestinal obstruction, diarrhea and renal failure, which may be associated with autonomic disorders.

BOTULISM

Next disease manifested by neurological disorders is botulism for which responsible is a Gram positive bacterium - *Clostridium botulinum* [57]. Similar to *Clostridium tetani*, it is rod-shape and also capable of producing spores. Bacterium growth in the human body is rare, but if this happens, the place of infection is usually wound, and the disease itself is called wound botulism. Most often we are dealing with intoxication by eating foods containing, produced by this bacterium and considered the strongest toxin in the world, botulinum toxin. It is believed that only 450g of this substance is sufficient to kill the entire world human population [58].

After toxin entering into the human body, regardless of how it was absorbed, in the intestines or in the wound, it is transported with body fluids to the cholinergic endings of neurons. Its target is the presynaptic membrane of alpha-motoneuron [59]. Botulinum toxin is not one substance as a toxin. Eight serotypes are known, but only one can't cause disease symptoms. Depending on the serotype, this toxin binds to one of the proteins forming the presynaptic membrane complex (SNARE), which is responsible for the fusion of the synaptic vesicle filled with acetylcholine with the neuron membrane. Degradation, because such action is caused by botulinum toxin, which is a protease, one of the SNARE proteins leads to inhibition of the release of acetylcholine and occurrence of symptoms [60, 61].

A characteristic feature of botulism is a set of clinical symptoms that consists of symmetrical cranial nerve palsy followed by symmetrical descending flaccid skeletal muscle paralysis, which can lead to respiratory failure [62, 63]. Symptoms of cranial nerve palsy are: paralysis of oculomotor muscles, eye accommodation disorders, which results in blurred vision and ptosis. Swallowing problems and dysarthria appear, which is associated with glossopharyngeal nerve paralysis, and facial paralysis is manifested by the inability to move the facial muscles

and mask face. In addition the symptoms from the autonomic system can occur: dry mucous membranes, low blood pressure, nausea and vomiting, constipation [64].

SYPHILIS

Syphilis symptoms can manifest in many ways, often reminiscent as other neurological diseases. There are early and late forms of syphilis. Initially attacked components of the nervous system are cerebrospinal fluid, meninges and blood vessels [65]. Patients may show symptoms such as headache, nausea, vomiting, neck stiffness, photophobia, and even convulsions, which are caused by the involvement of the meninges causing their inflammation [66]. Progression of meningitis can also cause disorders of sensation, spasticity and aphasia [67]. In this phase, syphilis can also cause uveitis, thus reducing vision [68]. In the late form of syphilis, structures such as the brain and spinal cord are infected. This state causes general progressive paralysis and tabes dorsalis, which are known as classic forms of nerve syphilis, which can be manifested through psychiatric symptoms [69]. Progressive dementia is manifested by general insufficiency, the beginning of which Sobhan et al. describe by occurrence of mood swings, among which we can also find signs of mania or depression. These people may also be affected by cognitive impairment due to changes in the temporo-parietal region, decreased appetite, energy and sleep disturbances. Those patients also have suicidal thoughts and psychomotor impairment, which can be present in up to 27% of them [70]. Other symptoms that characterize progressive dementia include dysarthria, muscle tremors, memory impairment and different cognitive functions [70]. The last of these, however, more often affects patients with tabes dorsalis, in whom we can observe the occurrence of ataxia, severe pain, impaired limb movement, bladder and bowel disorders, as well as visual impairment caused by optic nerve involvement [71].

RHEUMATIC FEVER

Rheumatic fever is a multi-organ inflammatory disease that occurs on an autoimmune basis as a complication of streptococcal angina. The first symptoms of the disease appear about 21 days after streptococcal throat infection. These include fever, arthritis, heart inflammation, skin lesions, and Sydenham's chorea. Chorea in rheumatic fever affects approximately 10-20% of patients and usually appears later than other symptoms of the disease [72]. It also happens that it may be the only symptom of rheumatic fever (chorea). Numerous cases have been described in the scientific literature in which chorea was the only clinical manifestation of rheumatic fever [73]. Chorea movements in rheumatic fever rely on involuntary, sudden, short, fast, unique and

aimless movements, which usually involve facial muscles, distal limbs, the torso and are more pronounced on one side of the body. In addition, concomitant muscular hypotension is also characteristic. It is interesting to note that chorea also has psychiatric symptoms that generally precede motor disorders. They occur in the form of emotional lability, attention deficit disorder, irritability, depression, anxiety disorder or obsessive compulsive disorder (OCD) [74]. OCD occurs in up to 70% of cases of Sydenham's chorea. During sleep, the intensity of movement symptoms decreases.

Chorea disappears without leaving marks, but some patients may have emotional lability, headache and obsessive compulsive behavior.

PANDAS

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) this is the full name of the condition that affects children who have previously been infected with group A beta-hemolytic *Streptoccocus*. Similarly to rheumatic fever, the phenomenon of antigenic mimicry can be observed. Researchers confirmed the association of this disease with the production of antigens against group A beta-hemolytic *Streptococci* and the occurrence of this disease. These antibodies show the cross reaction with brain basal ganglia leading to the development of disease symptoms [75]. Among these symptoms, obsessive compulsive disorder, tics, chorea, hyperresponsiveness, personality changes and deterioration of academic performance come to the fore. In addition to OCD disorders, children may exhibit emotional lability, excessive urination, anxiety, handwriting changes, personality changes, separation anxiety, eating disorders, anxiety, aggression, depression, hallucinations, dilated pupils [76]. The average age of onset of symptoms is 6-8 year old and the majority of patients are boys. The first reports of this disease appeared in 1998. Currently, the criteria for this disease were updated in 2017 and include:

1. the presence of tics and / or OCD according to the DSM-IV scale;

2. onset of neuropsychiatric symptoms before puberty;

3. sudden onset and / or wave changes, with increased intensity of symptoms, calming down after some time;

4. temporal association with Streptococcus infection;

5. hyperactivity, uncoordinated movements, chorea [77].

These criteria are still very controversial and some authors are skeptical about the occurrence of the PANDAS syndrome itself, convicting that this may be a different manifestation of such diseases as Tourette syndrome or Sydenham's chorea [78, 79, 80].

SUMMARY

Infectious diseases are a comprehensive branch of medicine dealing with the diagnosis and treatment of diseases caused by viruses, bacteria, parasites. Another area of interest is the neurological specialty that deals with diseases of the nervous system. This article combines issues from both of these fields of medicine. In their clinical practice, neurologists must demonstrate a wide range of knowledge, diagnostic and therapeutic skills for infectious diseases that have affinity for the nervous system. Moreover, these diseases do not always develop immediately and in the event of even rheumatic fever or Lyme disease do not always appear at the time of infection. Symptoms that appear as a result of the development of the diseases include these simple, non-specific symptoms such as weakness, abdominal pain, fever or headache to more serious, life-threatening as respiratory failure, arrhythmias. It is important to remember about the possibility of these diseases during the diagnostics of neurological conditions, which, however uncommon, can happen to anyone, regardless of whether you are a neurologist, internist or pediatrician.

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