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Neurological complications of infective endocarditis - a review

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Abstract

Introduction and purpose

Infective endocarditis (IE) is a disease resulting from infection of the endocardium. In addition to cardiac symptoms, frequent complications of IE include various damage to the nervous system.

The aim of this study is to describe the current state of knowledge about the neurological complications of infective endocarditis.

Methods

Medical publications were reviewed using the "PubMed" and "Google Scholar" databases. The obtained results were verified in terms of the following criteria: publication in 2016, retrospective analysis, obtaining 44 papaers covering a total of 8067 patients. The information was supplemented with case reports and meta-analyses.

Description of the state of knowledge

Neurologic complications occur in 20 to 60% of patients with IE. The most common is ischemic stroke, the symptoms of which may precede the diagnosis of IE. Less common complications that often remain asymptomatic include mycotic aneurysms and intracranial hemorrhages. Infectious material entering the brain may also cause meningitis and brain abscess. However, these complications do not occur often. Magnetic resonance imaging of the head is an effective test for detecting neurological damage in the course of IE. The recommendation for routine use of this test is debatable. In addition to antibiotic therapy, cardiac surgery is used to treat IE to remove bacterial vegetation. Research indicates the high effectiveness of this type of surgery in the prevention and treatment of neurological complications of infective endocarditis.

Summary

Neurological complications are an important element of the overall clinical picture of patients with infective endocarditis. Further research is necessary to better explore appropriate diagnostic and therapeutic methods.

Key words: infective endocarditis, neurologic manifestations, stroke, intracranial hemorrhage, surgery, imaging

Introduction and purpose

Infective endocarditis (IE) is a disease resulting from infection of the endocardium, usually in the valves, ventricles, atria, the endothelium of large blood vessels in the chest (e.g. narrowed aortic isthmus), vascular connections or foreign bodies in the heart, such as

pacemaker electrodes [1] Most often, IE affects the heart valves: aortic and mitral. Due to the most common cause of IE - bacterial infection - the basis of treatment is antibiotic therapy. Complications occurring in the course of IE include primarily embolism, metastatic infections, heart failure, and renal failure [2]. Infective endocarditis may also cause various neurological complications. The most common is ischemic stroke, but patients also have other symptoms of nervous system involvement: intracranial hemorrhage, mycotic embolism, meningitis or brain abscess [3]. Diagnostic and therapeutic difficulties are caused by both the correct detection of neurological complications and the selection of the right time for possible implementation of surgical treatment [4].

The aim of this study is to describe the current state of knowledge about neurological complications occurring in infective endocarditis, their frequency, diagnostic methods and treatment strategies.

Methods

A review of the current scientific literature was performed from the following databases: PubMed and Google Scholar using the keywords "infective endocarditis" and "neurologic complications", "stroke", "intracranial hemorrhage", "surgery" and "imaging", combining them with the modifier "AND". ” - e.g. (infective endocarditis) AND (stroke). From the obtained results, retrospective studies were selected analyzing the course of IE with specific neurological complications and the effectiveness of methods for detecting and treating these complications. The information presented in this paper is based on 44 retrospective studies published in 2016 or later, conducted on a total of 8,067 patients. The information was supplemented with conclusions from reports of single clinical cases (n = 4) for issues where there are no such studies, and with data from meta-analyses (n = 1) - chart 1. It is marked in the text if a study other than a retrospective one is cited.

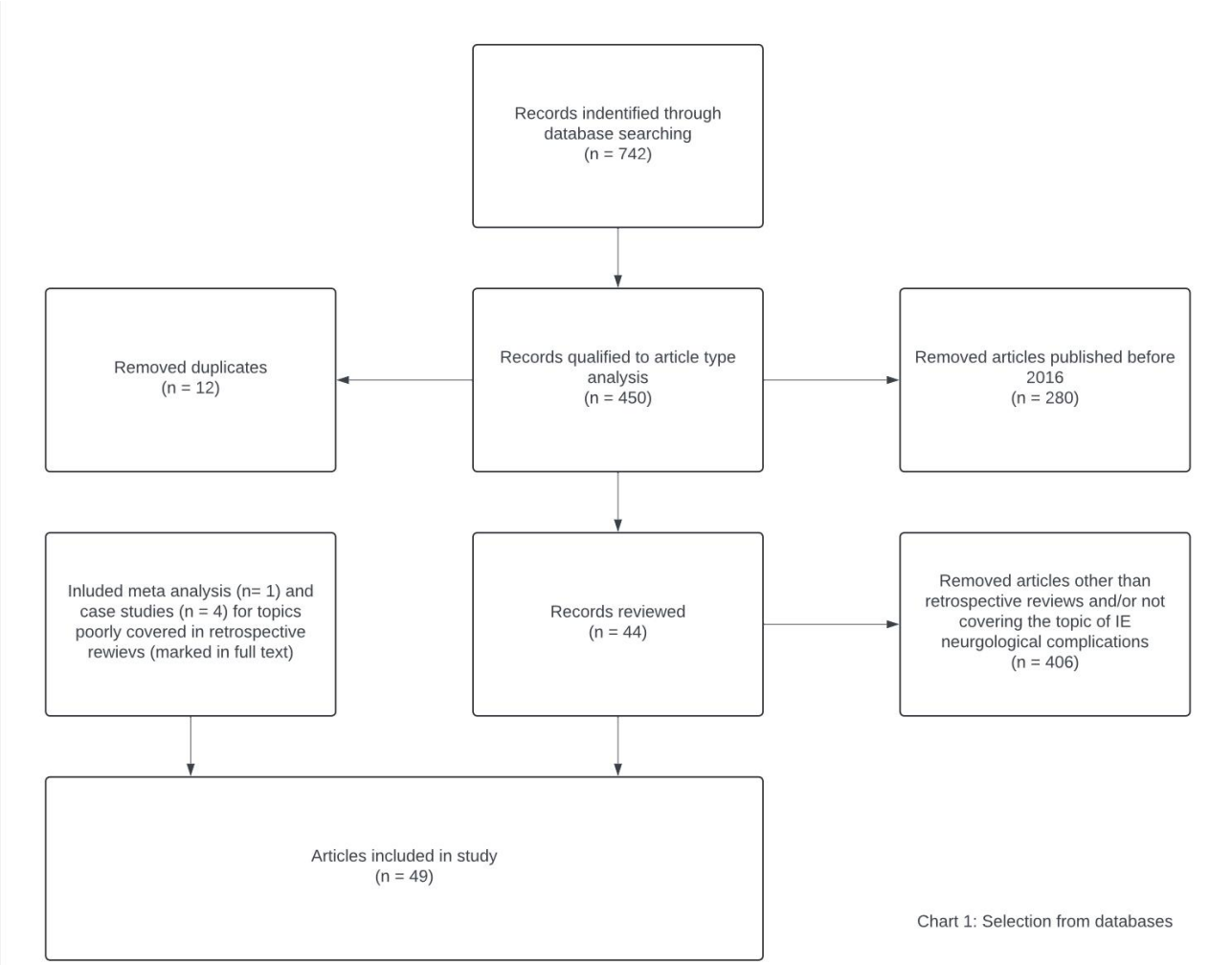

Chart 1: Selection from databases

Description of the state of knowledge

Stroke and risk factors for neurological complications

Neurologic complications occur in 20% to more than 60% of patients with infective endocarditis [5-8]. The most common is ischemic stroke, occurring in approximately 27% of all patients with IE [8,9]. The bacterial infection that develops on the heart muscle tissues increases blood clotting and promotes the formation of clots, which can then clog the vessels supplying blood to the brain [10]. This risk is increased if the patient has emboli outside the nervous system [6,9]. Additionally, biofilm fragments may separate from the vegetation on the valves and enter the cerebral circulation, blocking its vessels - vegetation size ≥15 mm and left-sided IE are associated with an increased risk of stroke [9,11,12]. In patients who

have had IE, residual vegetation >5 mm is associated with a higher incidence of ischemic stroke after recovery from endocarditis [15]. A recent study by Aydin et al. showed that the Glasgow prognosis score calculated based on the level of albumin and C-reactive protein in patients may be an independent predictor of ischemic stroke in patients with IE [14]. Sometimes neurological symptoms may precede the diagnosis of IE in a patient [15]. In addition to the size of the vegetation, the following risk factors for neurological complications include: early admission to hospital (<10 days from the onset of symptoms), duration of antibiotic therapy less than 7 days before the onset of neurological symptoms, and chronic steroid therapy before valve surgery [16]. A study by AlBassri et al. conducted in a pediatric group indicates low body weight, changes in the left heart valves and a high level of inflammatory parameters as risk factors for neurological complications of IE in children [5]. The presence of risk factors may increase the likelihood of stroke by up to twenty times [17].

Mycotic aneurysm and intracranial hemorrhage

Infected (mycotic) aneurysms are caused by the entry of infectious embolic material into the intravascular space or the network of small vessels and subsequent damage to the blood vessel wall with its segmental inflammation [18]. They are found in up to 32% of patients with infective endocarditis [19]. They are usually asymptomatic, but their rupture and subsequent intracranial hemorrhage can be potentially very dangerous. Studies indicate that patients with an infectious aneurysm have a higher risk of intracranial bleeding [20, 21], and bleeding resulting from a ruptured aneurysm significantly increases mortality in the group of patients with IE [22]. According to the analysis of Ragulojan et al., rupture occurs in approximately 36% of all patients with infectious cerebral aneurysms [23], much more often than in the case of extracranial aneurysms [24]. Digital subtraction angiography is more sensitive in detecting cerebral aneurysms than classic computed tomography and magnetic resonance angiography [19]. Endovascular therapy is highly effective in the treatment of mycotic aneurysms. Closure of the parent artery or embolization of the aneurysm reduces the risk of both intracranial bleeding [25] and intraoperative complications in cardiac surgical treatment of IE [26]. This procedure is more effective if it is performed early [24].

Rupture of an infective aneurysm is a common cause of another complication of infective endocarditis, namely intracranial hemorrhage (ICH). Depending on the place of blood extravasation, ICH is divided into epidural, subdural, subarachnoid hemorrhage (SAH)

and intracerebral [27]. The literature also uses the term microhemorrhages, defined as blood extravasations of a few millimeters in size - however, there is no evidence of their connection with the rupture of mycotic aneurysms [28]. Intracranial hemorrhages occur with a frequency of approximately 7-27% of all cases of IE [3,29]. Studies indicate that from 15% to 40% are caused by transformation from an ischemic lesion [18,30]. The causes also include infection of the brain tissue parenchyma and vasculitis [31]. Risk factors for ICH include a long period of fever, ineffective antibacterial treatment [32] and thrombocytopenia, severe heart valve regurgitation [31] and Staphylococcus aureus infection [3], which, especially in the case of methicyllin-resistant S. aureus strains, is associated with a higher risk of death [33]. The most common symptoms of intracranial hemorrhages in the course of IE are: focal neurological deficit, headache and encephalopathy. The study by Khoury et al. shows that 19% of hemorrhages are clinically silent [31].

Meningitis

One of the complications of infective endocarditis is meningitis. It occurs when the pathogens causing IE penetrate the cerebrospinal fluid and start to multiply there. The inflammation may then spread continuously to the brain tissue, which significantly increases the risk of permanent neurological damage [34]. Due to the relatively rare occurrence of this complication of IE (approximately 2% of patients with meningitis is also diagnosed with IE), data on it in the literature are limited [35]. The study conducted by Béraud et al. indicates several key aspects of IE complicated by meningitis. Co-occurrence of infection of heart tissue and the central nervous system is rare but usually has severe course. Patients diagnosed with infective endocarditis who present neurological symptoms should be additionally examined for developing meningitis, and in patients in whom the treatment of meningits is ineffective, IE should be excluded [36]. Additionally, case reports published in the literature seem to suggest that it is often the complication of meningitis that is diagnosed first, even though the primary source of infection is endocardial vegetation [37-40].

Brain abscess

A brain abscess is a focal infection of brain tissue. This infection may spread continuously or hematogenously, even from distant primary sites such as the endocardium.

Initially, an inflammatory infiltrate is formed, which disintegrates after about two weeks, forming a reservoir of purulent content surrounded by a thin-walled, well-vascularized bag. The abscess is surrounded by a zone of cerebral edema [41,42]. Brain abscesses in the course of infective endocarditis develop mainly in young people taking intravenous drugs. Additionally, the risk of abscess occurrence is higher in the case of concurrent meningitis, infection caused by a rare pathogen, and if extracerebral abscesses are present. HIV infection, alcohol abuse, liver disease and type 2 diabetes were also observed more often in people with IE and intracranial abscess [43]. Brain abscesses can be identified in head imaging tests: computed tomography (CT) and magnetic resonance imaging (MRI), with MRI being more sensitive, especially in the case of small lesions [44]. MRI may sometimes be the only way to detect a brain abscess, because a significant proportion of them (65%) remain asymptomatic [43].

Routine detection of neurological complications in magnetic resonance imaging

Head imaging studies, apart from the patient's clinical picture, are a basic tool for assessing neurological complications occurring in infective endocarditis. The most effective tool for detecting changes in nervous tissue is magnetic resonance imaging (MRI). It can visualize changes such as ischemia, subarachnoid hemorrhage, interstitial hemorrhage, and infectious aneurysm, which effectively complement the information obtained from computed tomography and the clinical picture of the patient [45,46]. MRI is also effective in detecting asymptomatic brain lesions [18]. The importance of MRI has increased since the presence of brain lesions in patients without neurological symptoms was added to the small Duke criteria - general brain MRI now influences the diagnosis of IE [47]. The validity of performing a review MRI in patients with a diagnosis of IE but without neurological symptoms remains the subject of research. Such changes are found in up to 70% of patients [48]. They may be a reason to perform surgery or modify its date and scope, e.g. additional surgery on an asymptomatic mycotic aneurysm [49]. Modifications may also include pharmacotherapy, for example changing the treatment to only anticoagulants, adding antifungal drugs or adding antibiotics that penetrate the peripheral nervous system [50]. On the other hand, many studies suggest no significant clinical improvement in neurologically asymptomatic patients who routinely underwent MRI. The following are noted: no impact of head MRI results on therapeutic decisions [51], good survival of patients after surgery, regardless of the results of

head imaging [52, 53] and the lack of a significant impact of routine MRI on the treatment outcome [54]. In their meta-analysis, Champey et al. state that MRI creates a new perspective for the treatment of complicated IE, but there are no sufficient scientific grounds to recommend its routine use [55].

The impact of cardiac surgery on the course of the disease in patients with neurological complications

Surgical treatment of infective endocarditis focuses on restoring normal heart anatomy, removing bacterial vegetation, and repairing and replacing heart valves. It is associated with risk: studies report in-hospital mortality reaching 15-25% and annual mortality exceeding 45% [56]. At the same time, researchers indicate the effectiveness of surgery in the treatment of IE with neurological complications. Particular attention is paid to the time needed to implement surgical treatment. The data suggest that early surgery is more effective than postponing surgery, especially if the patient's disease course is severe and/or neurological complications are serious. The European Society of Cardiology in its 2023 guidelines defines urgent surgery as performed within 3-5 days of the diagnosis of IE. Procedures performed after 4 weeks from diagnosis are considered deferred [48]. Additionally, studies indicate good effectiveness of surgical treatment in several specific groups of patients. Patients with septic embolism and septic shock benefit from this, although the development of sepsis itself worsens the prognosis of IE [57]. Similarly, early surgery is effective in patients with ischemic stroke [58], especially if the area of ischemia is small [59]. If a mycotic aneurysm is detected, it may be important to protect it endovascularly before making a decision about cardiac surgery [60]. However, a study conducted by Shi et al. suggests that surgical and conservative treatment of IE in the presence of an aneurysm is characterized by similar effectiveness [61]. If a patient with IE suffers from intracranial hemorrhage, better results are achieved when surgery is postponed for a few days [62], but the occurrence of ICH itself does not result in postoperative exacerbation of the patient's condition or an increase in postoperative mortality [63]. The study by Salaun et al. indicates that the mortality rate of patients with ICH is higher if, despite indications, surgery is not performed due to hemorrhage and conservative treatment is used instead [30].

Summary

Neurological complications of infective endocarditis still pose a diagnostic and therapeutic challenge. A number of predisposing factors contribute to their occurrence, including the large size of bacterial vegetation and the presence of artificial valves. While these factors translate causally into the development of neurological complications - they increase the risk of contact of infectious material with the nervous system - researchers draw attention to another, less specific risk factor, which is intravenous drug use [64], which may have future more important than those mentioned above. Among the known complications of IE, the most common is ischemic stroke, the symptoms of which may precede the diagnosis of endocarditis. An effective treatment method is classic thrombectomy [65]. However, special attention should be paid to patients with neurological deficits and fever in order to correctly diagnose their primary cause, which may be endocarditis.

Mycotic aneurysms are a relatively rare complication, but they can potentially lead to very dangerous intracranial hemorrhage. If detected, the patient can be effectively protected against rupture with endovascular treatment. It is necessary to localize the aneurysm first, but most patients are asymptomatic, which may cause diagnostic difficulties. Intracranial hemorrhages also often result from transformation from an ischemic lesion. Nearly 20% of them are also clinically silent, and many patients have multiple microhemorrhages. The presence of extravasated blood in the skull cavity is one of the few indications for postponing cardiac surgery in the case of co-occurrence with infective endocarditis.

Data on IE complicated by meningitis are limited. As in the case of ischemic stroke, the diagnosis of IE may precede the diagnosis of IE in the patient. Another rare complication, brain abscess, is associated with intravenous drug abuse and remains asymptomatic in most cases.

If neurological complications of IE are suspected, a head imaging examination should be performed [47]. The fastest and most available test is usually computed tomography. Compared to CT, magnetic resonance imaging is a more accurate examination, detecting more small lesions, including asymptomatic ones. Further research is required to determine the appropriateness of routinely performing MRI for brain imaging in the presence of neurological complications of IE.

Treatment of infective endocarditis is based on antibiotic therapy and surgery, mainly focused on removing bacterial vegetation. Research indicates that early surgery is more

effective in the treatment of IE than antibiotic therapy alone. Delaying cardiac surgical intervention is recommended only in a few specific cases, for example the presence of intracranial bleeding. Patients with various neurological complications benefit from surgery.

Further research is necessary to deepen the topic of neurological complications of infective endocarditis. Their limitation, similarly to this work, may be the fact that this disease does not occur often and the analysis of a larger group of patients often involves the need to qualify cases from a very long period of time, during which the availability and quality of the tested diagnostic methods and technologies change.

Statement of the authors‘ contribution

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Methodology: Paweł Stanicki

Software: Paweł Stanicki, Julita Szarpak, Aldona Pażyra, Natalia Kusak, Natalia Żak, Barbara Jaworska

Check: Paweł Stanicki

Formal Analysis: Paweł Stanicki, Julita Szarpak, Aldona Pażyra, Natalia Kusak, Natalia Żak, Barbara Jaworska

Inestigation: Paweł Stanicki, Julita Szarpak, Aldona Pażyra, Natalia Kusak, Natalia Żak, Barbara Jaworska

Resources, data curation: Paweł Stanicki, Julita Szarpak, Aldona Pażyra, Natalia Kusak, Natalia Żak, Barbara Jaworska

Writing- rough prepaton: Paweł Stanicki, Julita Szarpak, Aldona Pażyra, Natalia Kusak, Natalia Żak, Barbara Jaworska

Writing- review and editing: Paweł Stanicki

Supervision: Paweł Stanicki

Project administration: Paweł Stanicki

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