MIGRAINE: A COMMON DISEASE WITH POSSIBLE DISASTROUS CONSEQUENCES

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ABSTRACT:

BACKGROUND: The World Health Organization (WHO) established a worldwide change on the view of migraine by stating it to be one of the four most disabling chronic medical disorders. Headache disorders bring along personal suffering, impaired quality of life and financial costs. There are two forms of migraine, migraine with aura (MA) and migraine without aura (MO). In 1975 the first correlation between migraine and ischemic stroke (IS) was observed with a twofold higher risk of developing IS in migrainous patients.
OBJECTIVE: The aim of this article is to summarize the known information of the mechanisms behind migraine. The well-described mechanisms behind migraine and stroke will lead to the development of future diagnostics and therapeutics to decrease the prevalence of migraine and strokes.
RESULTS: Migraine is caused by cortical spreading depression (CSD) which is a wave of intense nerve cell activity that spreads through an unusually large area of the cortex. This hyperexcitable phase, that may be caused by local elevations of extracellular potassium, is followed by a wave of neuronal inhibition. Inhibited neuronal cells require less oxygen and therefore cerebral blood flow decreases. The trigeminal nerve system carries nerve signals from meninges and these blood vessels and establishes pain sensation. Three possible pathophysiological mechanisms, by which migraine may induce a stroke, can be explained: cortical spreading depression, spasms of the large intracerebral arteries and hypercoagulability related to vascular endothelium dysfunction.
CONCLUSION: Future research on diagnostic and therapeutic tools on possible targets in these mechanisms has to be done to decrease the prevalence of migraine and eventually stroke caused by migraine.

WHAT IS KNOWN? The WHO states that migraine is one of the four most disabling chronic medical disorders.

WHAT IS NEW? An overview of the current literature containing the possible mechanisms, by which a stroke can be induced by migraine; cortical spreading depression, spasms of the large intracerebral arteries and hypercoagulability related to vascular endothelium dysfunction.

KEYWORDS: Migraine, Stroke, Cortical spreading depression

Introduction

Migraine still remains to be one of the most misunderstood, poorly recognized and mistreated medical disorders. These headaches have been considered imaginary for a long time and are only since a few decades recognized by physicians as a disease. Patients still believe physicians are skeptical towards migraine and therefore seek no medical consolation for their pain; only 30% of the patients suffering from migraine visits a PD in the Netherlands[1]. A report published by the World Health Organization established a worldwide change on the view of migraine by stating it to be one of the four most disabling chronic medical disorders[2]. In the past year 47% of the world population has had a headache of which 10% had migraine. Headache disorders bring along a great burden of disease including personal suffering, impaired quality of life and financial costs[3]. Many triggers are registered that could evoke an attack such as emotional stress or physical activity. Migraine arises from a dysfunction in the nervous system and most likely from the brainstem. There are two forms of migraine. One, migraine with aura (MA), involves sensory hallucinations which are not present in the other form, migraine without aura (MO). Aura often precedes an attack[2]. Migraine presents itself with a great interindividual variety in frequency, duration and experience of the attack. Current research into migraine is focused on the involvement of genetics, imaging of the brain and molecular biology.

Migraine-related ischemia

Ischemic stroke (IS) is a cerebrovascular disease, often associated with migraine. The prevalence of IS is 1/500 in patients above the age of 65 years[4]. In 1975 the first correlation between migraine and IS was observed with a twofold higher risk of developing IS in migrainous patients. Studies including MRI brain imaging found an increase of IS in the posterior circulation territory in migraine patients. Furthermore, women with migraine have a higher risk of developing white matter lesions[5].
The association between migraine and stroke has proven much more complex than initially recognized, especially because a number of vascular disorders can cause both MA and IS. Moreover, cerebral ischemia can trigger MA. Epidemiological studies have reported an association of migraine (mostly with aura) with ischemic stroke, hemorrhagic stroke, coronary events, and mortality[6,7]. Migraine can directly lead to a stroke, which is called a migrainous infarction, or an indirect relation exists when a stroke occurs during the time between migraine attacks. Therefore, it is of importance to further clarify the underlying mechanism of migraine to be able to identify a mechanism by which migraine increases the risk of getting a stroke. Finally, the discovered mechanism between migraine and stroke will lead to the development of future diagnostics and therapeutics to decrease the prevalence of migraine and also strokes[8]. This review is constructed of literature on underlying mechanisms causing migraine and the association with cerebral stroke.

The inclusion for articles was based on impact factor, the use of English language, primary or secondary publications, number of times the article was cited, date of release and relevance.

Pathophysiological mechanism of migraine

To elucidate the possible mechanisms of migraine causing stroke, it is important to have a clear idea of the mechanisms underlying migraine. This disorder has an extensive history of hypothetical mechanisms containing vascular causes and a dysfunction of the trigeminal nerve. The most acknowledged hypotheses and how they can cause the typical migraine symptoms is elaborated below.

Cause of aura

Aura is caused by cortical spreading depression (CSD). CSD is a wave of intense nerve cell activity that spreads through an unusual large area of the cortex, especially the occipital cortex which controls vision. This hyperexcitable phase is followed by a wave of neuronal inhibition that can be seen on fMRI or EEG. During this phase of inhibition the neurons are non-excitable. Patients experience bright hallucinations, which can be explained by the excited state of neurons, followed by dark spots, which can be subscribed to the inhibition of neurons. When neurons are excited the need for oxygen increases which reflects in an increased cerebral blood flow (CBF). In the inhibited phase the demand for oxygen decreases, explaining the CBF changes. The electrical waves move extremely slowly: two to three millimeters a minute while normal nerve action potentials travel with speeds of 120 meters per second. This rate of spread probably explains why the aura is seen first, before the actual pain starts to set in. The posterior parts of the brain, primarily the occipital lobe, are initially affected. When the spread has reached the central sulcus, the pain starts to set in[2].

Trigeminovascular nociception

The pain during a headache is established by a network of nerves, called the trigeminal nerve system, which carry nerve signals from meninges and blood vessels. These nerves signal to the trigeminal nucleus in the brainstem and from there the signal is conveyed up through the thalamus to the sensory cortex. Which mechanism activates the trigeminal nerve is under debate. The first hypothesis states that CSD activates this pathway directly via a wave of increased neurotransmitter and ion release. Patients without aura have a CSD activation that is present on sites of the cortex or on subcortical regions that do not produce recognizable symptoms. Other researchers claim that the genesis of pain is placed in the brainstem. There is evidence that three nuclei, the locus coeruleus, raphe nucleus and periaqueductal gray, in the brainstem are active during and after a migraine attack. These nuclei could fail in inhibiting signals from trigeminal nerves as they are oversensitive to signals and can even send pain signals without any input[8].

Migraine considered as a channelopathy

Three gene mutations (in the CACNA1A, SCN1A and ATP1A2 genes) are associated with migraine. These genes encode neuronal ion channels and pumps. Mutation in those genes could cause channelopathy which can be responsible for getting migraine. It is believed that CSD is caused by local elevations of extracellular potassium [K+] which causes a decrease in K+ gradient, consequently causing a more positive membrane rest potential . Small changes in current can trigger an action potential and in this way get the cell in a hyperexcitable state[9] . The level of cortical excitability, which modulates the susceptibility to CSD, varies within the population. The level of excitability is low in people without migraine and high in patients with MA[8].

Pathophysiological mechanisms of migraine causing stroke

Three possible pathophysiological mechanisms, by which migraine may induce a stroke, can be explained: cortical spreading depression, spasms of the large intracerebral arteries and hypercoagulability related to vascular endothelium dysfunction[10]. These are the most fundamental mechanisms with sufficient evidence supporting these theories and they are elaborated below.

Cortical spreading depression

The mechanisms by which CSD may cause stroke remain purely hypothetical. In patients with migraine, inhibition of neurons can decrease CBF. This reduced flow can be decreased to such a low rate that dangerous ischemic levels could be reached with stroke as an effect. Currently, the medication that is given to patients with migraine have a rapid effect on arresting migraine attacks. These medicines work as a vasoconstrictor on the cerebral blood vessels and increase the risk of stroke, because it makes the chance of blockage of the vessels more prominent. Another theory described in this study is that a low threshold for CSD, that characterizes the brain in MA, also lowers the threshold for cerebral ischemia. There is some evidence for this theory that has been gathered by doing experiments on mice, but it remains controversial if this is plausible[8].

Vasospasm

In the past, before the mechanism of CSD was known, migraine was thought to be a vascular disease. For this reason the found literature underlying vasospasm is often outdated. Vasospasm, one of the possible mechanisms by which migraine can cause a stroke, is related to the vascularity of the brain. This theory suggests that by vasoconstriction of the intracerebral arteries, ischemia in the affected region and aura in the patient occurs[11]. A response of hyperaemia follows, leading to vasodilatation and headaches: a common symptom of migraine. Another dated article written by Cole et al.[12] assumes that during a migraine attack the cerebral blood flow diminishes, resulting in ischemia in the cells of the vasa vasorum (smaller blood vessels that perfuses the walls of the bigger blood vessel). This could develop necrosis of the endothelial cells and possible rupture of the cell wall when perfusion is restored. In migrainous cases, these patients show different possible causes of vasospasm. Vasospasm may have an underlying cause not related to migraine which will be disregarded as it is not a point of interest in this review. Another possible mechanism in which migraine is related, is that drugs which are given to migrainous patients can provoke vasospasm, such as ergotamine. The outbreak of arterial vasospasm can be due to substances as endothelin and serotonin. Although the distribution of vasospasm does not correlate with the affected area of the neurological effects of a migraine attack, it can be suggested that vasospasm is a side effect of migraine and it can be seen when a migrainous infarction occurs[9,12].

Hypercoagulability

Different studies show an increased production of platelet activating factor (PAF) during a migraine attack in MO patients. The sources of this PAF production are the endothelial cells in the brain and the mast cells[13]. PAF can trigger thrombotic cascades, as can be seen in figure 1, and is one of the most important molecules in causing hypercoagulability. There are several mechanisms correlating migraine with cerebral ischemia via hypercoagulability. Firstly, the activation of PAF causes accumulation of platelets to stop the bleeding when endothelial cells are damaged. When platelets are overactivated, it may result in ischemic stroke[14]. Secondly, PAF causes the release of von Willebrand factor (vWF), which is an important protein in coagulation. The primary function of

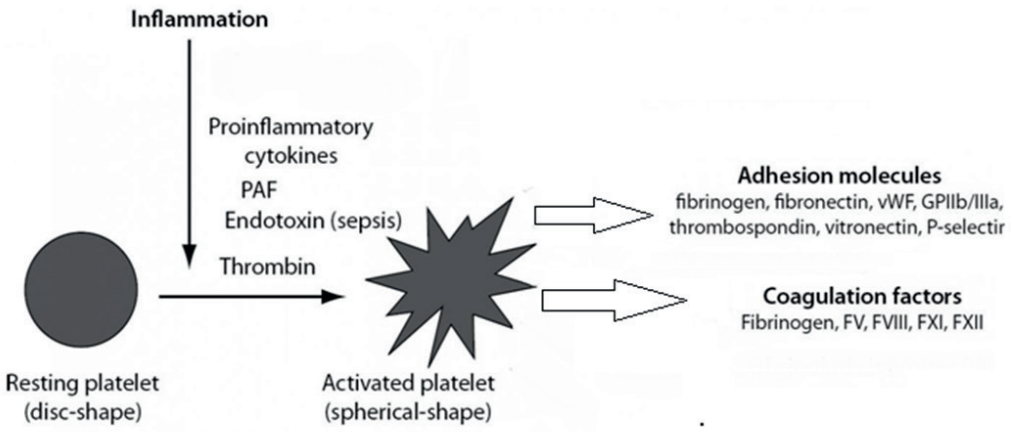

Figure 1 *Schedule with different proteins which are involved in inflammation and platelet activation*

vWF is to bind other proteins involved in blood clotting, in particular factor VIII, which is an important platelet adhesion molecule. A small study in people with migraine has shown a release of vWF during migraine[15]. This study did not examine whether this can also lead to an increase in hypercoagulability in migraine patients. Inflammation can be caused by platelets for the following reasons. Firstly, in a study from Taffi R et al., migraine patients show a significantly greater production of peroxynitrite (ONOO-) in their platelets compared to the production of ONOO in the platelets of controls. Furthermore, patients showed an increased expression of inducible Nitric Oxide Synthase (iNOS) in comparison to control subjects. iNOS can react to peroxynitrite which is a marker for oxidative stress[16]. Oxidative stress can cause endothelial cell death and results in inflammation by activating the PAF pathway. This inflammation can lead to more hypercoagulability via platelet activation. The platelet activation causes an increase in many different proteins and molecules like adhesion molecules and coagulation factors. A higher coagulability can cause blood clots which can block an artery and cause stroke.

Discussion

Although there is a substantial amount of research on migraine and stroke, the studies used in this review had some limitations. A lot of studies that were done examined different proteins and whether the concentrations of these proteins were elevated in migraine patients compared to controls. Unfortunately, the relationship between the different proteins was not well defined in these studies. Moreover, no evidence was found for the correlation between the elevation of these proteins and the onset of stroke. The mechanism underlying migraine is just a hypothesis, so the mechanism which describes the relation between migraine and stroke can only be postulated in the following plausible summarized theories. Cortical spreading depression is one of the underlying mechanism how stroke can be caused by migraine. During CSD the blood flow decreases and can even reach ischemic levels, so a stroke can occur. On the other hand, controversy remains over the actual establishment of pain in CSD. The underlying mechanism of CSD and pain is therefore still questionable. A possible way in which vasospasm can provoke a stroke can be explained according to the vascular theory. This theory asserts that vasoconstriction of the intracerebral arteries during a migrainous attack cause ischemia in that specific area which can result in a stroke. The second pathway of a stroke inducing mechanism is in the cells of the vasa vasorum. Ischemia can result in necrosis of the vasa vasorum and possibly rupture of the entire blood vessel wall when perfusion is restored. When endothelial cells are damaged, PAF activation leads to accumulation of platelets. It is well known that overactivation of platelets can cause stroke. Also PAF induces the release of the von Willebrand factor which leads to blood clotting. There is also an increase in production of peroxynitrite and induced nitric oxide synthase, which are both markers for oxidative stress. After oxidative stress development cell death may ensue, which can cause inflammation. Inflammation can be a source of hypercoagulability. Blood clotting can be an important cause of strokes, because it can block the vessels, which could have cerebral ischemia as an effect.

Recommendations

Several mechanisms and proteins are involved in migraine causing a stroke. Future research on diagnostic measures and therapeutic interventions on these possible mechanisms has to be done to decrease the prevalence of migraine and eventually stroke caused by migraine. Several targets for therapeutic and diagnostic measures can be imagined based on the three mechanisms: CSD, spasms of the large intracerebral arteries and hypercoagulability related to vascular endothelium dysfunction. First of all, there could be a therapy for the CSD K+ ion-channel dysfunction, which is hard to target specifically. A possibility of a future diagnostic tool is to do genetic tests based on the three genetic mutations that encode the potassium channels and pumps. Patients with the genetic defect could get preventive stroke therapy or screened for other risk factors for stroke. During CSD a critical level of CBF can be reached what may result in cerebral ischemia. A population at risk in migraine patients could be formed which would include patients with a cardiovascular background, obesity or a reduced vascular plasticity for example. With this information preventive measures could be initiated to prevent strokes. Currently, medication is given to patients to immediately alleviate the pain symptoms. The medication, that has vasoconstrictor properties, should be used as little as possible as it increases the risk of stroke. Migraine patients have temporary lesions in the brain, a transient ischemic attack (TIA), which can be visualized by MRI[10]. These lesions are an indicator for having an increased chance of the development of stroke. Possibly, patients with suspected migraine can undergo a MRI-scan to confirm having migraine-related lesions and thus a higher stroke risk. A preventive therapy against migraine can be given to these early-diagnosed patients, which hopefully can prevent occurrence of a stroke. Unfortunately, this preventive therapy has not yet been developed, so further research on this therapy has to been done. Targeting vasospasm is hard because the exact mechanism of how vasospasms occur is not well known. It is not recommended to give vasoconstrictors or vasodilators because they respectively increase the risk of stroke or worsen the symptoms. Stroke caused by hypercoagulability could be reduced by providing patients with blood thinners. This hypothesis is based on the fact that blood that is thinned flows faster and has a lower probability

to clot. Because the risk of developing a blood clot is less prominent it is more unlikely to cause a stroke. These targets are hypothetical based on the mechanisms that are found and explained in this review. They all could be possible indications for further investigation. These investigations will hopefully give insight into this complicated and underdiagnosed disorder and prevent disastrous consequences.

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