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Diagnosis and treatment of migraine: an analysis of the latest diagnostic and therapeutic guidelines

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Abstract

Introduction

Migraine is a common disease that a large part of the population struggles with. Stressful work and poor eating habits increase the risk of headaches. The basic therapy is lifestyle change, and when this does not bring results, medications are used. The choice of the appropriate preparation depends on the characteristics of the pain and the patient's condition. Knowledge about different treatment methods can improve patients' lives.

Aim of the study

The aim of the article was to present current guidelines for migraine therapy depending on the individual patient's requirements.

Materials and methods

The article is the result of a review of recent scientific literature using PubMed, Scopus and Google Scholar databases. The literature was reviewed using the keywords.

Results

Many clinical trials have examined the effects of different classes of drugs on migraine headaches. The final effect depends on the dose used, the moment of drug administration, and the patient's age, gender and health condition. Doctors often have to modify therapy within the same group of drugs to find a drug that will work for a given patient.

Conclusions

Clinical trials have proven the effectiveness of, among others, non-steroidal anti-inflammatory drugs, triptans and botulinum neurotoxin. A clinically significant analgesic effect is sometimes characterized by side effects, therefore careful selection of the preparation and patient observation are important.

Key words: botulinum neurotoxin; non-steroidal anti-inflammatory drugs; migraine; triptans.

Introduction

Migraine is a common neurological disease characterized by recurrent, spontaneous headache. It affects approximately 17% of women and 9% of men, and women are more often diagnosed with migraine without aura than with aura.

In Poland, approximately 2.5 million people struggle with this condition. The annual incidence rate is 11.7%, which places it in the top ten diseases with a negative impact on health. The incidence of migraine in prepubescent girls and boys is the same. In adults, migraine usually begins between the second and third decade of life. The first migraine episode occurs in 90% of patients before the age of 40, and only in about 3% after the age of 60. Most cases of migraine occur before the age of 35, peaking between the ages of 30 and 40. [1]

Migraine pain is described as a recurrent, severe, throbbing headache. It is often accompanied by autonomic symptoms: nausea, vomiting, hypersensitivity to light and noise. There are two main clinical forms: with and without aura. In approximately one third of patients, headaches are accompanied by symptoms of visual aura, nausea and vomiting,

photophobia and hypersensitivity to light and sound. Migraine patients show a constant readiness to develop an attack that occurs throughout most of the patient's life, with a variable individual frequency of occurrence. Typically, 1-3 attacks occur per month, and an untreated attack lasts on average 18 hours. Patients do not experience any symptoms between pain attacks. Important features of migraine are the diversity and variability in the clinical picture, both between individual attacks and during the disease. As the disease progresses, progression into chronic migraine or daily headaches is observed in some patients (in approximately 10% of patients), as well as changes in electrophysiological recordings and white matter. We talk about chronic migraine when the pain occurs for at least 15 days a month, of which at least 8 are days when the headache meets the criteria for the diagnosis of migraine and persists for at least the next 3 months or disappears under the influence of triptans or ergotamine and arose from a type of headache. headache that previously met the criteria for episodic migraine without or with aura. [2]

The costs incurred by society due to migraine are significant. In Europe, they are estimated at approximately EUR 1,222 per year per patient, which, with approximately 41 million patients, gives the total of EUR 55 billion per year. It is worth emphasizing that, according to the US Migraine Cost Study, approximately 300,000 people miss work every day due to a migraine attack. Other analyzes conducted in Great Britain and the USA have shown how much migraine affects the daily lives of sufferers. Migraine is a serious disruption to personal and professional life, causing limited contact with family and friends and changes to family and social plans. Additionally, a person suffering from this condition may often miss work due to migraine attacks, which can lead to absences of 2 to 4 days per month. During a migraine attack, the patient takes on average 2.5 tablets of the drug. Migraine is known to be underdiagnosed, which means that many patients do not receive appropriate treatment. Only one third of people with migraine regularly seek medical care. [1,3]

The pathogenesis of migraine has not yet been known. It is postulated that excessive contraction and subsequent dilatation of cerebral vessels, including the arachnoid, accompanied by hyperperfusion and angioedema, are associated with the secretion of pro-inflammatory neuropeptides, including calcitonin gene-related peptide (CGRP), substance P, neurokinin A and nitric oxide. These substances cause a condition of sterile arachnoiditis. The initial phase of migraine is associated with the brain stem, where the centers of the nociceptive system are located, initiating a change in neuronal and vascular activity in the brain called cortical spreading depolarization (CSD). Research also shows an important role

of the first branch of the trigeminal nerve in the development of migraine. Currently, the genetic background and the undoubted influence of the external environment are little known - the involvement of up to 200 different genes involved in the pathogenesis of migraine is currently postulated. Epidemiological studies indicate a predisposition to migraine with aura in people with the C677T methyltetrahydrofolate reductase gene mutation. Both migraine with and without aura may occur episodic or chronic. A migraine attack has five phases: prodromal, aura, pain, resolution, and postdromal. [4,5]

Treatment

Migraine is a recurrent and episodic disease for which there is currently no single effective drug. The therapy focuses primarily on improving the quality of life of people affected by the disease. Inadequate treatment of migraine may result in the disease turning into a chronic form. Appropriate therapy includes non-pharmacological and pharmacological options. [6]

Non-pharmacological methods of treating migraine

Lifestyle factors such as sleep, eating habits, stress, and exercise are associated with the occurrence of migraines. A study conducted on 350 migraine patients showed that people who eat poorly, do not care about sleep hygiene, do not cope with stress and do not exercise regularly have a greater risk of developing an episodic migraine into a chronic one.

The first therapeutic step in a patient with migraine should be to create a headache calendar, enabling the assessment of when and in what situations the pain occurs; In women, hormonal fluctuations may also have an important impact on pain episodes. According to the guidelines defining non-pharmacological treatment of migraine, the following is recommended:

1. Regular rest periods at night, as improving and extending sleep can reduce the frequency of migraine attacks.
2. Hydration, because inadequate water intake is one of the causes of migraines.
3. Physical exercise - there is a lot of scientific evidence that regular physical exercise reduces stress levels and, therefore, reduces the risk of a migraine attack. In one study involving 91 migraine patients, one group of people performed physical exercises three times a week for 40 minutes, while the other group of participants took topiramate (an antiepileptic drug, also used to prevent migraine headaches) at the highest tolerated dose. As a result, when comparing the two groups participating in the study, there were no statistically significant differences in the reduction of migraine pain.

4. Diet. Eating certain foods can lead to a migraine attack. Prohibited foods include chocolate, ripened cheeses, alcoholic beverages and those containing caffeine.
5. Relaxation therapies - yoga. One clinical study proved that relaxation techniques allow for better control of migraine pain, while at the same time enabling the reduction of medications consumed. [7-8]

Pharmacological methods of treating migraine

One of the most important aspects of migraine therapy is learning to recognize and characterize the pain that occurs. In the event of a migraine attack, it is necessary to react quickly and take the desired medication to avoid the development of pain and end the attack. The drug should be selected depending on the severity of symptoms, possible route of administration, and taking into account the presence of comorbidities in the patient. [9]

Nonsteroidal antinflammatory drugs

Non-specific treatment, focused on the symptoms, is based on the administration of an analgesic - paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs), such as acetylsalicylic acid (ASA), ibuprofen, diclofenac, and dexketoprofen. These medications are available without a prescription and can independently control mild migraine attacks. Paracetamol, due to its lack of anti-inflammatory effect, is a less effective drug, so it should be used in people with contraindications to the use of NSAIDs. It is also recommended for pregnancy migraine and in children. [10-11]

Dopamine D2 receptor antagonists

Adjunctive medications help control additional symptoms that often co-occur with migraine. Patients suffering from nausea or vomiting will be treated with neuroleptics (dopamine D2 receptor antagonists) with anti-emetic properties, such as: domperidone, metoclopramide, chlorpromazine. When using the drugs mentioned, you should monitor thepotential extrapyramidal side effects and concern overpotentially permanent tardive dyskinesia, andorthostatic hypotension and sedation. [12-13]

Triptans

Causative drugs are used to treat moderate or severe migraine attacks - these are triptans. Triptans are agonists of 5HT1B/1D receptors and act specifically on the cause of migraine by constricting blood vessels, which inhibits the migraine attack. Their safety and effectiveness have been proven in many clinical studies. When using triptans, blood pressure values should be monitored as they may increase. These drugs are contraindicated in people with uncontrolled hypertension, coronary artery disease, and peripheral vascular disease. Side

effects that may potentially occur after taking a triptan include heart palpitations, chest tightness and taste disturbances. Currently, there are 7 triptans available on the market, and the choice of the appropriate one must be determined individually based on the duration of migraine occurrence (night or day), its severity, frequency and accompanying additional symptoms (nausea, vomiting). Triptans can be combined with NSAIDs; Moreover, apart from standard tablets, other forms of the drug are available, such as injections or nasal sprays, which provide a much faster effect. [14-15]

Sumatriptan

The best-studied triptan to date is sumatriptan, which first appeared on the market in 1993. It is available in 100 mg and 50 mg tablets, 25 mg suppositories, 12 mg/ml pre-filled syringes and 200 mg/ml nasal spray. Its effect was comparable to the combination of a NSAID - 900 mg of acetylsalicylic acid and 10 mg of metoclopramide. Paracetamol at a dose of 1000 mg in combination with 130 mg of caffeine also showed a similar effect to sumatriptan. Sumatriptan was also compared to the non-steroidal anti-inflammatory drug naproxen at a dose of 500 mg. Interestingly, the combination of these two drugs resulted in a better result than using them separately. Another NSAIDs - ibuprofen at a dose of 400 mg was as effective as sumatriptan at a dose of 50 mg. Sumatriptan is considered an older generation drug and is often used as a reference to other triptans. [16-18]

Eletriptan

Eletriptan is another triptan that is commonly used in the treatment of migraine. Both eletriptan and sumatriptan were more effective than placebo in clinical trials. The 80 mg dose of eletriptan was superior to sumatriptan. Both drugs have comparable safety. When using eletriptan, it was found that the occurrence of migraine recurrences was less frequent compared to sumatriptan. It was hypothesized that patients who did not respond to sumatriptan treatment or were unable to use it due to side effects could try eletriptan. It has also been shown that the use of eletriptan in situations where the intensity of pain is mild provides significantly greater results compared to situations when the pain is moderate or severe. The effects of eletriptan have also been correlated with those of zolmitriptan. More patients responded to treatment with eletriptan compared to the group treated with zolmitriptan. Another triptan that eletriptan has been combined with is naratriptan. It was shown that eletriptan also had an advantage in terms of the percentage of patients who responded to treatment. Additionally, taking eletriptan was less frequently associated with the occurrence of recurrent headaches; side effects were similar. [19-21]

Frovatriptan

Studies on frovatriptan showed that the optimal dose is 2.5 mg. Higher doses showed similar effectiveness, but their use was associated with a higher rate of side effects. This triptan has not been combined with sumatriptan. In one study, frovatriptan was combined with dexketoprofen (NSAID), which increased its potency and brought better results than frovatriptan alone. Another clinical trial compared the effects of several triptans in people who experienced between 1 and 6 migraine attacks per month. In one study, frovatriptan 2.5 mg was combined with rizatriptan 10 mg; in the second study, frovatriptan at the same dose was compared with 2.5 mg of zolmitriptan, while in the third study, frovatriptan was compared with 12.5 mg of almotriptan. The first three migraine episodes were treated with frovatriptan, and the next three with another triptan mentioned earlier.

The effectiveness of the drugs used and patients' preferences for various triptans were similar. The main difference noticed was a significant improvement in the recurrence of headaches. Frovatriptan proved to be the best in this respect, probably due to the longest half-life. Therefore, its use turned out to be the most economical. More and more studies indicate that frovatriptan may be the first-line drug in migraine therapy. [16, 22-24]

Almotriptan

Almotriptan is a drug that has recently appeared on the Polish market and is available over the counter in only one dose - 12.5 mg. In one clinical study, 12.5 mg of almotriptan was combined with sumatriptan 50 mg. Both drugs were used to treat moderate to very severe migraine headaches. Ultimately, both preparations showed very similar effectiveness. It was also found that if sumatriptan is ineffective, almotriptan may be a very good alternative. On this basis, the thesis was once again put forward that different types of triptans can be used in different patients, and a specific drug should be selected very carefully and individually based on the greatest possible good of the patient, taking into account effectiveness, tolerability and side effect profile. Almotriptan was also combined with frovatriptan described above. Here, also two hours after taking the drug, similar effectiveness in eliminating headache symptoms was demonstrated. There is currently no significant evidence in the scientific literature for the combination of almotriptan with NSAIDs. [16, 25-27]

Zolmitriptan

Zolmitriptan in Poland is available in the form of tablets in two doses: 2.5 mg and 5 mg. There is also an intranasal form on the market, which is particularly effective in cases of very severe pain, morning migraines or migraines with co-occurring vomiting. Zolmitriptan 5

mg was compared with sumatriptan 50 mg. It was shown that pain recurred less frequently after the use of zolmitriptan, which is probably related to its favorable pharmacokinetic profile. Among patients using both drugs, greater preference was given to zolmitriptan. When comparing zolmitriptan 2.5 mg with frovatriptan 2.5 mg, complete headache relief was more common in patients treated with frovatriptan. Relief of existing pain and headache recurrence were comparable in both drug groups. Another triptan with which zolmitriptan was combined was naratriptan. These triptans were compared at the same dose: 12.5 mg. The effects and side effects were similar for both drugs. A comparison of 2.5 mg zolmitriptan and 10 mg rizatriptan showed that more patients were headache-free with rizatriptan two hours after administration. It is also worth mentioning the combination of 2.5 mg zolmitriptan with 80 mg eletriptan, where eletriptan turned out to be a more effective drug; however, a dose of 40 mg of eletriptan had similar effectiveness to 2.5 mg of zolmitriptan. [16, 28-30]

Naratriptan

Naratriptan is available in two variants: 1 mg tablets and 2.5 mg tablets. It has been shown that a higher dose is definitely more effective than a lower one. However, it is worth noting that the lower dose turned out to be effective in the prevention of menstrual migraine when the drug was used twice a day for 6 days a month. Naratriptan was compared with the effects of rizatriptan 10 mg, sumatriptan 100 mg and eletriptan 40 mg. Each of these drugs turned out to be more effective than naratriptan, while zolmitriptan at a dose of 2.5 mg was similar to naratriptan. Naratriptan 2.5 mg was found to be an alternative to sumatriptan treatment. A 16-year study was also conducted on patients in the first trimester of pregnancy. The effects of naratriptan, sumatriptan and both drugs were compared in a group of 52 pregnant participants. A major congenital defect was found in only one newborn exposed to sumatriptan and naratriptan. [16, 31-33]

Rizatriptan

This medicine is available as 10 mg tablets, including rapidly disintegrating tablets. Various doses of rizatruptan (2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg) were studied in clinical studies. The most effective dose was 40 mg; unfortunately, it was also characterized by the most common side effects. Rizatriptan has also been proven effective in the treatment of menstrual cycle-related migraine headaches. It is worth noting that studies have shown that rizatriptan 10 mg was better than sumatriptan 100 mg in many respects. In a comparison of rizatriptan and zolmitriptan, rizatriptan was more effective in eliminating headache 2 hours after taking the drug. In turn, a dose of 2.5 mg of frovatriptan was comparable to 10 mg of

rizatriptan. Rizatriptan turned out to be a stronger drug than ibuprofen at a dose of 400 mg. The simultaneous use of 10 mg of rizatriptan and 1000 mg of paracetamol gave more favorable results than the administration of paracetamol alone. It is also worth noting that the best results from taking rizatriptan were noticed in the early phase of pain onset. For the vast majority of triptans, there are no data on the use of these drugs in children. Rizatriptan was tested in children aged 6-17 years, where the following doses were effective: 5 mg in children weighing less than 40 kg and 10 mg in children weighing more than 40 kg. [16, 34-36]

Botulinum neurotoxin

A modern approach to migraine treatment is botulinum toxin (registered under the popular trade name Botox®), a protein substance produced by the Clostridium botulinum bacteria. According to current statistics, botulinum neurotoxin is effective in improving the quality of life of patients and in reducing the number of days with migraine; however, it is probably not effective in the case of tension headaches. The mechanism of the analgesic effect of botulinum neurotoxin is not well understood. It is likely that this drug works by blocking the release of inflammatory mediators and pain mediators from the trigeminal nerve endings. Thanks to this, it is possible to long-term anesthesia of the hypersensitive trigeminal nerve endings and to inhibit the reactions leading to pain. Often, the drug is not effective when administered once (injected), so the process must be repeated, which leads to a reduction in the severity and frequency of migraine attacks. Botulinum neurotoxin gained popularity thanks to one of the clinical trials of 1,384 patients, where one group of people was treated with botulinum neurotoxin, while the other group took a placebo. There were significant clinical differences in favor of the drug group, with a reduction in the number of days on which migraine occurred, the duration of pain and the number of doses of triptans taken. The study also showed that early initiation of botulinum neurotoxin therapy is more beneficial than treatment in the advanced phase of pain. [37-42]

Summary

Migraine is a chronic and very difficult to treat disease. The recurrent nature of pain and its unexpected appearance significantly reduce the quality of life of sick people. Currently, there are many therapy methods available, which depend on the type of pain and the patient's individual preferences. In case of mild severity of the disease, drugs with anti-inflammatory properties are used. Moderate and severe disease activity requires primarily attempts at causal treatment, with triptans being the first choice. If patients have a contraindication or triptans

turn out to be ineffective, then modern methods become the therapy of choice - one of them is botulinum neurotoxin, which is gaining more and more supporters every year.

Disclosure

Authors contributions

Joanna Cieszkowska: Conceptualization, Writing - rough preparation, Methodology, Investigation, Project administration

Karina Otręba: Formal Analysis, Visualisation

Karolina Czupryńska: Software, Writing – review and editing.

Piotr Daniel: Methodology, Investigation

Michał Leśkiewicz: Supervision, Resources

Justyna Aleksandra Składanek: Supervision, Data curation

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Conflict of Interest Statement

All authors declare that they have no conflicts of interest.

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