MIGRAINE: PATHOPHYSIOLOGY-BASED TREATMENT APPROACHES

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Introduction

The management of migraine patients comprises various dimensions that have to be adapted to the patient's profile and to the clinical diagnosis. The psychological dimension, for instance, has a crucial role in headache patients for a number of reasons among which psychiatric co-morbidity. I will focus here on validated drug and non-drug treatments in migraine, but also on strategies for which there is only class IV evidence available. As a matter of fact, the statement that "evidence-based medicine is not cookbook medicine" applies particularly well to migraine and can be underscored by three examples which I will illustrate. First, several anti-migraine treatments are in use since decades and have not been assessed in trials with up-to-date satisfying methodology. Second, novel pharmacological strategies will be tested in large and costly multi-centre trials only if a company expects a commercial benefit, which is not the case for low cost, not-patented substances. Third, meta-analyses have shown differences between drugs by comparing the results of separate placebo-controlled trials for each of them; such differences are not always confirmed in direct comparative trials of two drugs because of the variable placebo response.

Migraine pathophysiology is complex and may differ between patients, probably because of genetic differences. While the common final pathway of the migraine attack seems to be the trigeminovascular system (TGV), the factors upstream leading to activation of this system may vary and include cortical spreading depression, at least in migraine with aura, dysfunctioning limbic and pain control centres and disequilibrium between neurono-glial energy reserve and cortical responsivity. This schematic pathophysiological framework explains why overall acute antimigraine treatments have higher efficacy scores than available preventive therapies.

Acute treatment

Attack treatments are thought to act within the TGV and possibly its central pathways. The triptans, agonists of the 5-$HT1_{B/D}$ receptors, were a breakthrough in acute migraine therapy. Oral triptans, however, are superior to well-dosed NSAIDs mainly for severe attacks. Whereas the efficacy differences between the various oral triptans are small and patient-dependent, the efficacy score and speed of action is clearly superior for the injectable form of sumatriptan, but at the expense of a higher incidence of adverse effects. CGRP is a pivotal neurotransmitter in the TGV. Recently, drugs blocking CGRP receptors or CGRP itself have opened a new area. The gepants, non-peptide anatgonists of CGRP receptors, are as effective as oral triptans and have the advantage of being devoid of vascular effects. Unfortunately their development was halted because of hepatotoxicity. The most promising agents presently in phase II-III trials are monoclonal antibodies directed against CGRP or its receptor. First results are tantalizing since 1 or 2 injections per month seem to be able to decrease durably attack frequency. An important complication of acute antimigraine treatment is headache chronification by medication overuse. Medication overuse headache can be diagnosed if the patient uses triptans, ergotamine or combination analgesics on ≥10 days per month, or simple analgesics on ≥15 days per month. Migraineurs who develop this complication and tend to relapse may have hypo-activity in the medial orbito-frontal cortex, which is also found in substance abusers.

Preventive treatment

The major problems with anti-migraine prophylactic treatments are relative lack of efficacy (50% on average), side effects for many drugs and, partly as a consequence of the former, poor compliance. The most rapidly acting drugs in migraine prophylaxis are certain anticonvulsants (valproate & topiramate), beta-blockers devoid of intrinsic sympathico-mimetic activity, serotonin- (methysergide) or calcium (flunarizine) antagonists. Unfortunately, these are also the drugs with the highest incidence of adverse effects among which the CNS effects often aggravate symptoms which are highly prevalent in migraineurs such as depressive mood, fatigue, daytime sleepiness, attention deficits or overweight. Other preventive drugs are less potent but have much fewer side effects. This is the case for the sartans and some nutriceuticals, like riboflavine or co-enzyme Q10. The latter are supposed to partly correct the deficit ATP content that characterizes the migrainous brain between attacks. Interestingly this metabolic deficit may depend on variants in the non-coding portions of mitochondrial DNA. The therapeutic response to riboflavin, for instance, is better in patients having the non-H haplotype. Because of the complex pathophysiology of migraine, combination of different prophylactic agents is a plausible strategy, but still lacks evidence-based data.

Cognitivo-behavioural treatments (relaxation therapy with or without biofeedback, auto-hypnosis..) which are the mainstay in tension-type headache management, may also add value to pharmacologic treatments in migraine. By contrast, it has been shown in various RCTs that homeopathy and acupuncture are not better than placebo that may have a remarkable and long lasting effect in migraine.

Given the poor efficacy-side effect ratio of most preventive anti-migraine therapies, there is room for alternative treatments. Neurostimulation methods, in particular, have been applied to migraine treatment in recent years. Non-invasive peripheral nerve stimulation (PNS) has virtually no side effects and can be applied to any migraine patient in need for prevention. The portable supraorbital nerve stimulator Cefaly° was found superior to placebo for migraine prevention and promising results are available also for the transcutaneous stimulator Gammacore° of the vagus nerve in the neck. Invasive peripheral neurostimulation must be restricted to the most disabling patients. Percutaneous occipital nerve stimulation, for example, provided partial relief for chronic migraine patients in some trails, but not in all. Chronic migraine is also the only migraine subtype where multiple pericranial injections of Onabotulinum toxin A are slightly, but significantly superior to saline injections in a proportion of patients. Considering the complex pathophysiology of chronic migraine and its comorbidity, an integrative treatment strategy based on the combination of several treatment modalities has the best chances of success.

Transcranial magnetic or direct current neurostimulation methods allow a pathophysiologically driven treatment approach in migraine, as they have the potential to modify brain functions that are found to be abnormal between attacks. Proof-of-concept trials were positive for both treatment modalities in episodic and chronic migraine prevention.

Conclusion

To conclude, the possibilities for effective management of migraine have improved over the last decade. For the acute treatment there is a need for more efficient oral drugs and for safer drugs. There is much to gain with more efficient and better-tolerated prophylactic anti-migraine treatments. The fact that different pharmacological classes of anti-migraine prophylactics have on average only 50% efficacy is most likely due to the complex and heterogeneous pathogenesis of migraine. Therapeutic progress is therefore dependent on a better understanding of migraine mechanisms and genetics, and thus on clinical and basic research.