

Tempo Medical

Headaches and migraines : the contribution of neurostimulation

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12 % of the population suffers from migraine and prophylactic treatment with medications is often required. As pointed out by Professor Jean Schoenen, Director of the *Unité de Recherches sur les Céphalées* (Headache Research Unit) of the University of Liege, the most effective treatment is still topiramate (Topamax®), with an average response rate of 45 %. This means that 55 % of patients do not respond. Furthermore, half those suffering from migraine complain of significant side effects, to the extent that 25 % of those for whom the molecule is prescribed give it up. A further point : most chronic migraine sufferers these patients suffer more than 15 days of headache per month – become resistant to drug treatment. It is clear therefore that neurology is confronted with a lack of effective prophylactic treatments for migraine, so much so that there is

plenty of room for approaches that could serve as an alternative to medications.

Noninvasive neurostimulation (Cefaly®) : PREMICE study

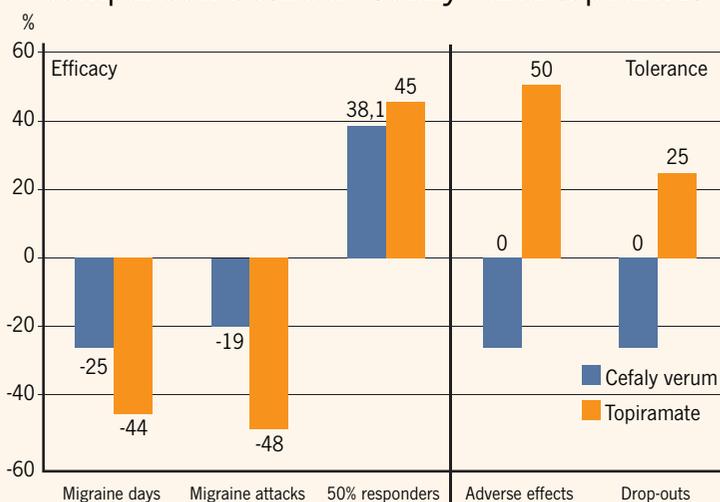
For several years now we have been witnessing the emergence of treatment by neurostimulation. At the symposium Professor Bart Vandersmissen of the *Université libre de Bruxelles* (Free University of Brussels) presented the results of the clinical study PREMICE (*Prevention of Migraine by supraorbital transcutaneous neurostimulation using the Cefaly® device*). Directed by Professor Schoenen, this multicentre study was conducted in five major neurology departments of the country by specialists who are members of the Belgian Headache Society. A randomised, doubleblind study, it involved 67 patients, of whom 34 were given real transcutaneous stimulation of the supraorbital and supratrochlear nerves and 33 sham stimulation.

Designed and developed by the Liege company STXMed, the stimulator, called Cefaly®, resembles a diadem. This is attached to a self-adhesive electrode placed on the forehead, through which very precise impulses are transmitted to the nerve endings of the superior branch of the trigeminal nerve, the visceral part of which innervates the meninges (the trigeminovascular system) and is strongly involved in migraine. The stimulation, lasting 20 minutes per day, can be increased in intensity up to around twenty milliamps.

A few years ago a pilot study conducted by the Professor Schoenen's research unit highlighted a certain preventative effect of Cefaly® on migraine attacks. This effect has been confirmed by the PREMICE study, as Bart Vandersmissen points out. After three months of treatment a reduction of 50 % or more was found in the number of days of migraine in 38,1 % of patients in the Cefaly® group, while this benefit was only recorded for 12,1 % of patients in the placebo group. The consumption of medications for migraine attacks, such as triptans, dropped by 37 % in the Cefaly® group, while it remained practically unchanged in the placebo group. In the responders to the neurostimulation treatment this reduction was close to 75 %.

The efficacy of Topamax® remains higher, but the Cefaly® technique has the advantage of having no side effects and for this reason it can be associated with a drug treatment.

Efficacy and tolerance : comparison between Cefaly® and topiramate



The exact action mechanism of Cefaly® is not known. Jean Schoenen, together with researchers from Brussels, demonstrated that the treatment had a slight sedative effect. Furthermore, FDGPET studies carried out in association with the *Centre de Recherches du Cyclotron* (Cyclotron Research Centre) of ULg (University of Liege) have shown that, in chronic vascular pain of the face (or cluster headache), suboccipital neurostimulation by subcutaneous electrodes (see below) acts on the descending paincontrol pathways, but does not change the hyperactivity of the hypothalamus, which is thought to be at the origin of the attacks. An action purely on the symptoms therefore. According to Jean Schoenen the most likely hypothesis is that the action of Cefaly® is of the same type : the stimulation of the trigeminal afferent pathways reaching the brain and brainstem alters the activity of the centres which belong to the "migraine neuromatrix" and contribute to the control of migraine pain.



Invasive neurostimulation

a) Occipital nerve

Let us now consider the second topic of the symposium : a review of data published concerning the stimulation of the occipital nerve in chronic migraine. Speaker : Professor Koen Paemeleire of the University of Ghent. Deep stimulation of the hypothalamus was given up because of the risks of intracerebral haemorrhage. At present the focus is on less risky types of stimulation, in particular suboccipital stimulation. An

electrode is implanted under the skin near the greater occipital nerve ; it is coupled with a stimulator similar to a pacemaker which is placed prepectorally and discharges continuously. In chronic cluster headache resistant to drug treatment, this technique has proved effective in some 70 % of patients. While the attacks disappear completely in certain patients, very few are able to give up treatment with drugs completely.

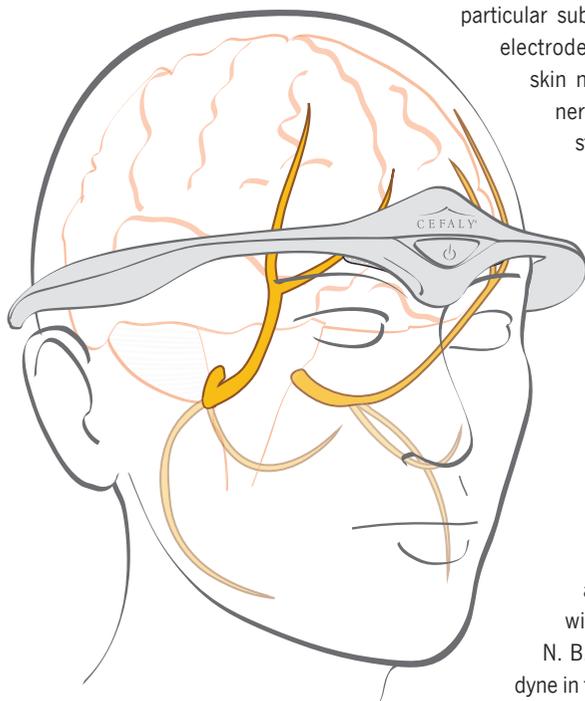
N. B. : the method is not anodyne in that its implementation requires a general anaesthetic and com-

plications (particularly infections) are possible. Furthermore, the continuous nature of the stimulation disturbs some patients because it gives rise to paraesthesias.

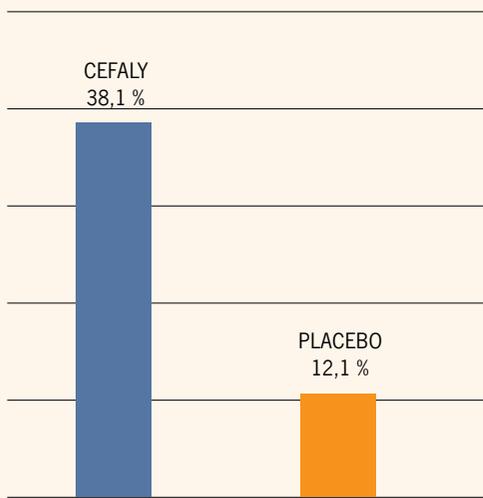
Two American studies of suboccipital stimulation in chronic migraine have been published. In these, unlike the procedure applied for cluster headache, implantation was bilateral. Positive results were obtained in 40 % of patients suffering from chronic migraine resistant to prophylactic drug treatment.

b) Sphenopalatine ganglion

In *cluster headache* the sphenopalatine ganglion plays a crucial role in the onset and sustaining of the attacks. In the wake of the work done in Las Vegas in 2010, a multicentre European study conducted by the Headache Research Unit (ULg) in patients with a chronic form of the disease looked at highfrequency stimulation of the sphenopalatine ganglion using a microstimulator implanted in the sphenomaxillary fossa. The results ? 70 % of the attacks stopped within fifteen minutes of the start of stimulation. It also appeared that in certain patients the greater the stimulation of the sphenopalatine ganglion, the greater the reduction in the frequency of the attacks. This ganglion is also involved in migraine. Professor Schoenen's team intend to test the abovementioned technique in severe migraine as well.



Cefaly efficacy



Patients' percentage having a reduction of at least 50 % of the monthly frequency of the crises of migraine

The future would seem to lie in combined supraorbital and suboccipital stimulation.

Non-invasive approaches

The third approach considered at the symposium dealt with the new perspectives opened up by noninvasive neurostimulation methods (transcutaneous) in migraine. Dr Delphine Magis (ULg, CHR de la Citadelle (Citadelle Regional General Hospital) gave an overview.

In addition to Cefaly®, presented above, the STX-Med company is now developing an external suboccipital stimulator. The University of Liege will soon examine the physiological and therapeutic significance of this. In fact, the future would seem to lie in combined supraorbital and suboccipital stimulation. In the framework of the CWALity projects of the Walloon Region the ULg and STX-Med are envisaging the possibility of designing an instrumentation system which would carry out this double stimulation transcutaneously. Combined supraorbital and suboccipital stimulation experiments using implanted electrodes have been described in the literature. The results obtained were better than those with stimulation focused on a single target.

Another approach referred to by Delphine Magis : transcutaneous stimulation of the vagus nerve. In refractory epilepsy implanted stimulators were effective in 30 % of patients treated. Now there is comorbidity, probably of genetic origin, between epilepsy and migraine. Experiments carried out in the rat, in cephalic pain and migraine models, by the Headache Research Unit brought to light a significant effect for stimulation of the vagus nerve delivered by an implanted stimulator. Nonetheless, up to the present no placebocontrolled (sham stimulation) clinical study has been undertaken in migraine patients.

Pilot trials have also been conducted using transcutaneous stimulation of the vagus nerve in the neck. This has been found to be effective in interrupting the migraine attack, but the attacks recommenced about ten minutes later.

Another possibility : a neurostimulator placed in the external acoustic meatus with its action directed at the auricular branch of the vagus nerve which innervates this canal. Animal studies show that this method of stimulation of the vagus nerve has antalgic effects.

A final research avenue : transcranial stimulation, the aim being to alter the excitability of the cerebral cortex of the migraine sufferer in the areas in which it is abnormal. As indicated by Jean Schoenen transcranial stimulation, either magnetic or by direct current, makes it possible to activate the areas that are hypoactive and inhibit those that are hyperactive. A study on the prevention of attacks by activation of the visual cortex is taking place at the University General Hospital of Liege.

The equipment necessary for transcranial magnetic stimulation is fairly substantial. So the treatment sessions must be carried out in a hospital centre. An alternative is transcranial directcurrent stimulation, requiring equipment which in theory is transportable. The Liege researchers have recently shown in a pilot study that, applied 2 to 3 times a week, this technique reduces the frequency of migraine attacks. For the moment all treatment is carried out in hospital, the idea being, however to develop equipment that the patient could use at home. This is the result that Professor Schoenen's group and the STX-Med company have set out to achieve. ■

References

D. Magis, J. Schoenen, *La neurostimulation : quelle place dans les céphalées réfractaires ?*, Rev Med Liège 2011 ; 66 : 2 : 8590

Further reading :

César FernandezdelasPeñas, Leon Chaitow and Jean Schoenen, *Multidisciplinary Management of Migraine*, Jones & Bartlett Learning, 2012, 441 p.