

Therapeutic neurostimulation in chronic headaches: problems of patient selection

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Abstract Chronic daily headache that does not respond or no longer responds to prophylaxis is commonly encountered at specialist headache centres. Animal and brain imaging studies indicate that peripheral neurostimulation affects brain areas involved in pain modulation, providing a rationale for its use in these conditions. We examine problems related to the selection of chronic daily headache patients for peripheral neurostimulation. These conditions are often associated with analgesic (including opioid) overuse, and psychiatric or other comorbidities, and the terms used to describe them (chronic migraine, transformed migraine, chronic daily headache and chronic tension-type headache) are insufficiently informative about these patients when proposed for neurostimulation. Longitudinal studies indicate that pre-existing subclinical depressive and anxious states play a key role in chronicisation and that the probability of responding to treatment is inversely related to headache frequency. These considerations suggest the need for extensive characterisation of patients proposed for neurostimulation. We propose that patients being considered for neurostimulation should be followed for at least a year, and that their headache over this time should consistently be frequent (all or most days) and drug refractory. We also propose that only *com-*

pletely drug-resistant (as opposed to *partially* drug-resistant) patients be considered for neurostimulation unless there are other indications.

Keywords Neurostimulation · Selection criteria · Chronic headache · Chronic migraine · Drug-resistant

Introduction

Migraine is common in western countries, with a prevalence of around 10%–15% [1]. It has been estimated to be the most costly neurological disorder in the European Community [2] and one of the most costly neurological disorders in the United States [3]. New therapies in headache are mainly driven by developments in migraine, and this is the case with peripheral neurostimulation, which has been proposed for the treatment of a number of drug-resistant primary headaches [4–8]. Animal studies indicate that peripheral neurostimulation can have an antidolorific effect (for review see Refs. 9 and 10) and may affect brain areas involved in pain modulation, providing a rationale for the use of these techniques in humans [7]. Over the last decade central (hypothalamic) stimulation has emerged as an effective new treatment for drug-resistant chronic cluster headache and other forms of trigeminal autonomic cephalalgia (TAC) (for review see Ref. 11). The introduction of this neurostimulation technique has raised a number of clinical problems regarding patient eligibility for the procedure, including whether the International Headache Society (IHS) definitions of chronic cluster and other TACs are detailed enough to appropriately select patients for neurostimulation [12].

Since neurostimulation is of growing interest as a treatment for drug-resistant primary headaches, we here

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examine some of the problems related to the selection for the technique of patients with chronic long-lasting (≥ 4 h) primary headache.

Selection for neurostimulation: focus on the headache or on the patient?

The classification published by the IHS [13] proved to be a landmark as it introduced for the first time a common language for headaches and reliable criteria for their diagnosis. Another result was that research into the causes and treatment of headache was greatly stimulated: neuroimaging studies investigated headache attacks, and triptans as treatment for acute neurovascular headaches (migraine and cluster headache) were developed and introduced.

The chronic forms commonly referred to as chronic migraine, transformed migraine, chronic daily headache and chronic tension-type headache remain difficult to classify and diagnose, and a widely used and accepted terminology is still some way off [14]. These forms are also more difficult to treat than episodic headaches, and this is the main reason why patients with severe chronic headaches are increasingly proposed for neurostimulation. The IHS defines these forms when headache is present for at least 15 days per month for the preceding three months [13, 14]. Patients undergoing neurostimulation or other surgery are usually characterised as having “chronic drug-resistant migraine” or “chronic daily drug-resistant headache” [6–8]. These terms encompass headache forms that can be highly heterogeneous in terms of pain localisation, duration and intensity, triggering factors, associated phenomena, association with hormone levels, age of onset, chronicisation pattern, duration of chronic form, etc. Furthermore, these chronic conditions are often associated with analgesic overuse, including opioids, and psychiatric or other comorbidities, including hypertension and cardiovascular disease [15]. Thus the terms chronic migraine, chronic daily headache and chronic tension-type headache are insufficiently informative about the generally complex clinical picture that characterises patients with chronic headache, particularly those proposed for neurostimulation.

Not even the clinical data used to assess the effectiveness of prophylaxis (number of days with headache, pain intensity, number of analgesics consumed, number of working days lost and headache-related disability) provide sufficient information about the patient to assess his or her suitability for neurostimulation.

Although mechanisms underlying the chronicisation of pain and headache are far from being fully understood, longitudinal studies indicate that pre-existing subclinical depressive and anxious states play a key role in chronicisation (for review see Ref. 15). It has also been found that

patients with chronic headaches tend to develop complex musculo-skeletal pain syndromes and such patients respond poorly to treatment [16]. Furthermore, the probability of responding to treatment is inversely related to headache frequency [16]. These findings, considered together with heterogeneity and complexity of the clinical pictures of chronic headache patients, suggest that extensive characterisation of those proposed for neurostimulation is necessary. This will allow identification of characteristics that distinguish responders from non-responders, and will in turn suggest hypotheses for prospective studies to identify factors that can guide patient selection.

Definition of chronicity for the purposes of selection for neurostimulation

The problem of the inadequacy of the IHS criteria as a guide to selecting patients for surgical procedures first arose when hypothalamic implant and stimulation was introduced to treat chronic cluster headache [17]. Most chronic cluster headache patients selected for surgery have daily attacks [18], yet the IHS criteria allow a diagnosis of chronic cluster headache when the patient has only 3–4 attacks per month over the preceding year [13] and this diagnosis is insufficient to select patients for surgery. The advantages and limitations of these criteria have been discussed elsewhere [12, 17, 18]. Regarding long-lasting (≥ 4 h) chronic headaches (chronic migraine, transformed migraine, chronic daily headache, chronic tension-type headache), all the available diagnostic criteria – those included in the IHS classification [13, 14] as well as in other classification systems [19, 20] – require that headaches should be present on 15 days or more per month for at least 3 months. The question arises as to whether headaches present for only 15 days a month and only for the preceding 3 months are sufficient to justify the invasive surgical procedure of neurostimulation. For example, a patient whose migraine has worsened to more than 15 attacks a month in the preceding 3–4 months may simply be experiencing a temporary period of exacerbation and should not therefore be considered for neurostimulation. Migraine is a fluctuating illness in which worsening and spontaneous improvements are not infrequent (for review see Ref. 16). It is also known that factors such as stressful life events, contraceptive pill use, hypertension, mood changes and the use or overuse of certain drugs can favour increase in headache frequency [16]. It seems reasonable therefore that patients fulfilling IHS criteria for chronic migraine (or more generally chronic daily headache) should be thoroughly investigated for the above factors, and where possible treated before considering any kind of surgery [21]. This approach to chronic daily headaches is usually only practised at specialist headache centres. However it is likely that neurostimulation will become available at other centres, and for this reason it is

important that widely accepted detailed criteria for selection for neurostimulation are developed and applied. Based on experience at our headache centre, we consider it reasonable to propose that patients being considered for neurostimulation should be followed for at least a year, and that their headache over this time should consistently be frequent (all or most days) and drug refractory (see below). Of course there may be exceptions, for example patients who are allergic, intolerant or have strong contraindications to several medications. The principle should be that each patient is evaluated individually and exhaustively by a multidisciplinary team (neurologists, psychiatrists, psychologists and neurosurgeons).

Another factor to be considered when evaluating chronic headache patients for neurostimulation is disability. Migraine – and even to a greater extent chronic migraine – may cause severe disability and reduction in quality of life [22]. However our experience is that many patients are able to lead fairly full social and family lives notwithstanding frequent headaches, because they are kept under control by the use of acute medications (analgesics, NSAIDs, triptans, etc.). We therefore propose that, in patients under consideration for neurostimulation, both disability score and number of analgesics/triptans taken should be considered.

Definition of drug-resistance for the purposes of selection for neurostimulation: *partial* and *complete* drug-resistance

Chronic daily headache patients who do not respond or who no longer respond to prophylaxis are commonly encountered in specialist headache centres [23]. The term drug-resistant can be applied to those who do not respond to one or more types of drug [24], as well as to those who do not respond to all known medications. In the former case the patient may well be responsive to one of the untried medications and we propose that *partially* drug-resistant be used for such cases, with *completely* drug-resistant used to specify patients who do not respond to *all* known medications [25]. We consider this distinction useful for assessing patients for neurostimulation and propose that only *completely* drug-resistant patients be considered for neurostimulation. All indicated drugs in the guidelines [25] or wider literature should be tried at adequate dose and for a sufficient period, and shown to be ineffective or associated with intolerable side effects unless contraindicated.

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