New treatment options needed for chronic cluster headache

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Most headache specialists have patients with chronic cluster headaches that are refractory to pharmacological prophylaxis. In desperation, some patients use subcutaneous sumatriptan for acute relief far more often than is recommended.[1] Occipital-nerve and deep-brain stimulation are therapeutic options, but the former is associated with lead migration, and the latter with potentially serious complications. Thus, more treatments are needed.

In *The Lancet Neurology*, Peter Goadsby and colleagues[2] report on a new, randomised, sham-controlled double-blind, parallel-group study of sphenopalatine ganglion stimulation as acute therapy in patients with chronic cluster headache. Their state-of-the-art trial builds on a previous smaller randomised study of the same sphenopalatine ganglion stimulator,[3] in which pain relief was achieved in 127 (67%) of 190 stimulation-treated attacks compared with 29 (8%) of 376 control attacks (ie, attacks in the same patients treated with either no stimulation or subperception stimulation). Blinding was a concern in that study, however, because patients experienced paraesthaesias with active treatment but no similar sensation during attacks treated with no electrical stimulation or with a subperception stimulus.

In Goadsby and colleagues' trial, which was rigorously designed to improve blinding, use of sphenopalatine ganglion stimulation over time not only provided acute relief of pain, but also seemed to reduce cluster attack frequency. The authors conclude that high-frequency sphenopalatine ganglion stimulation offers an alternative treatment approach that is efficacious, safe, and well tolerated in the context of a highly disabling condition. However, there are caveats that should be considered when interpreting the results of this trial. First, although Goadsby and colleagues' attempts to improve blinding were at least partly successful, participants in the active treatment group received electrical stimulation via the implanted neurostimulator and participants in the control group received cutaneous electrical stimulation via surface electrodes on the remote controller. Thus, the areas where paraesthesias were perceived were different. Blinding was assessed with the James' Blinding Index,[4] which is based on questionnaires in which participants or staff masked to treatment allocation are asked to indicate which treatment arm the participant is in. The score of 0·63 calculated by Goadsby and colleagues suggests adequate blinding (a score of 1·00 suggests complete blinding), but it is not clear whether the score applied to participants or masked staff. The protocol suggests that the participants were the people assessed. The degree of blinding obtained is important for accurate interpretation of the results.

Second, although cluster headache attacks are thought to arise in the hypothalamus, activation of the trigeminal–autonomic reflex, which runs through the sphenopalatine ganglion, is hypothesised by the authors to result not only in the parasympathetic autonomic features characteristic of cluster headaches, but also in the release of vasodilator peptides that activate trigeminovascular sensory fibres (via parasympathetic innervation of the cerebral vasculature)—a positive feedback that could initiate and sustain pain. Although this mechanism is plausible, the results of another study[5] suggest that sphenopalatine ganglion activation can induce the cranial autonomic symptoms of cluster headache but cannot induce the pain. If those findings are confirmed, the mechanism of how blocking neural activity in the sphenopalatine ganglion aborts the pain of cluster attacks would be difficult to explain.

Third, when Goadsby and colleagues used weighted generalised estimated equation logistic regression models to analyse their efficacy outcome data, sphenopalatine ganglion stimulation was estimated to lead to pain relief in 62% of attacks in patients in the active group, compared with 39% of attacks in patients in the control group. However, in unadjusted analyses, pain relief was achieved for only 189 (46%) of 410 attacks in the sphenopalatine ganglion group, compared with 226 (39%) of 582 attacks in the control group. The weighted approach was used to account for the nested data structure (ie, that each patient could have multiple attacks) and the fact that the expected number of treated attacks per patient varied greatly between patients. The model is probably appropriate for the data in this study, but the average reader is unlikely to be expert enough in statistics to form a judgment. Readers will therefore need to trust the expert authors, although the data analysis was done by the study sponsor. It is reassuring that independent statistical experts have peer-reviewed the report and agreed with the statistical methods used.

In summary, this study provides valuable evidence that sphenopalatine ganglion stimulation benefits patients with chronic cluster headache. Like most good studies, it raises new questions in addition to providing answers. Patients badly need more treatment options, and hopefully this therapy will be available in the near future, although the sponsor of this study has gone out of business because of financial issues, which could delay further developments.

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I have served on medical advisory boards and received speaker's honoraria from Allergan, Novartis, and Weber and Weber.

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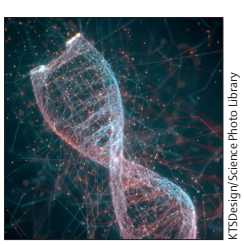
Challenges in disentangling the genetic background of Parkinson's disease

For more than two decades, it has been acknowledged that Parkinson's disease is genetically heterogeneous, and that large-scale studies are required to identify relevant genetic variants with small to modest effects.[1] The meta-analysis of genome-wide association studies (GWAS) of non-monogenic Parkinson's disease, reported by Mike Nalls and colleagues[2] in *The Lancet Neurology*, is the most comprehensive study to date on the genetic background of this complex disease. Clearly exemplifying the merits of large-scale aggregation of data, this work also illustrates some of the challenges in disentangling the genetic background of complex diseases.

The first challenge relates to the use of the results from GWAS for explaining heritability and informing genetic testing. Nalls and colleagues have identified 90 independent variants with promising functional associations; however, a large proportion of the heritability is still unexplained. This reduces the hope for the use of broad genetic testing in the near future, beyond the few Parkinson's disease genes that unequivocally have a causal role when mutated. To identify even more relevant variants, at least two avenues could be taken. The obvious method is to increase sample sizes even further to detect variants with yet smaller effects. However, the novel loci identified by Nalls and colleagues increased the odds for Parkinson's disease by as little as 1·05,[2] and to detect even smaller changes in risk, sample sizes of more than half a million individuals would be required. Another potentially promising method is to make use of the heterogeneity of Parkinson's disease and investigate subgroups defined by features such as age at onset and motor and other clinical characteristics,[3] as different phenotypic groups might have different genetic causes.[4] Given that, even within pedigrees, clinical features can differ to a relevant extent across carriers of the same familial mutation, selecting phenotypes that might be indicative of the cause will be an essential but difficult step. On a related note, extending the focus to less investigated ethnic groups is not only ethically mandatory, but also a promising lead to identify more underlying disease variants.

A second challenge of modern GWAS relates to the knowledge they provide on functionality and causality in complex diseases such as Parkinson's disease. GWAS originally set out to solve some of the problems of previous genetic epidemiological studies—such as difficulties in recruitment of families in linkage studies and risk of false-positive results in candidate association studies. However, one drawback of association studies compared with linkage studies is that an association can be caused also by other confounding factors, making it more difficult to show causality of the genetic loci. Indeed, the original hope that using single nucleotide polymorphisms as markers would directly identify the culprit via direct association has only seldom been fulfilled.[5] For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